BEFORE THE OIL CONSERVATION COMMISSION
COMMENCING NOVEMBER 12, 2024

CASE NO. 23580

WILD EARTH GUARDIANS – PFAS RULEMAKING

PART 4

NEW MEXICO OIL AND GAS ASSOCIATION

NMOGA EXHIBIT E11.499 THROUGH
NMOGA EXHIBIT E20.155

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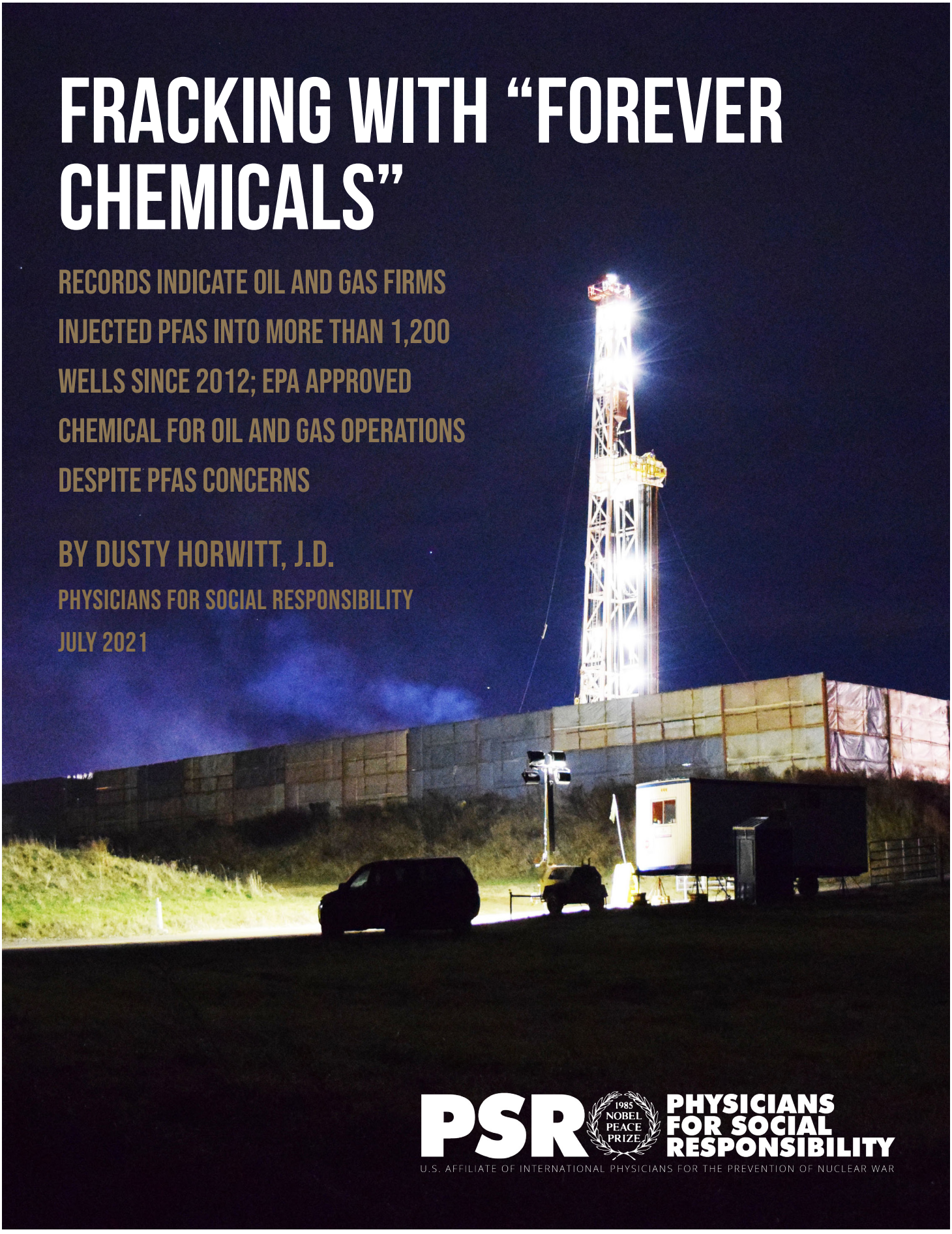
FRACKING WITH "FOREVER CHEMICALS"

RECORDS INDICATE OIL AND GAS FIRMS INJECTED PFAS INTO MORE THAN 1,200 WELLS SINCE 2012; EPA APPROVED CHEMICAL FOR OIL AND GAS OPERATIONS DESPITE PFAS CONCERNS

BY DUSTY HORWITT, J.D.

PHYSICIANS FOR SOCIAL RESPONSIBILITY

JULY 2021



PSR 1985 NOBEL PEACE PRIZE PHYSICIANS FOR SOCIAL RESPONSIBILITY

U.S. AFFILIATE OF INTERNATIONAL PHYSICIANS FOR THE PREVENTION OF NUCLEAR WAR

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EXECUTIVE SUMMARY

Evidence suggests that oil and gas companies including ExxonMobil and Chevron have used per- and polyfluoroalkyl substances (PFAS), or substances that can degrade into PFAS, in hydraulic fracturing ("fracking") for oil and gas in more than 1,200 wells in six U.S. states between 2012 and 2020. The lack of full disclosure of chemicals used in oil and gas operations raises the potential that PFAS could have been used even more extensively than records indicate, both geographically and in other stages of the oil and gas extraction process, such as drilling, that precede the underground injections known as fracking.

PFAS have been linked to cancer, birth defects, pre-eclampsia, and other serious health effects. Toxic in minuscule concentrations, they accumulate inside the human body and do not break down in the environment – hence their nickname, "forever chemicals." PFAS were widely used for decades in non-stick cookware, stain-resistant carpeting, fire-fighting foam and other products before their highly toxic characteristics became public around the year 2000. Chemical manufacturers Dupont and 3M had known about these chemicals' environmental and health risks as early as the 1960s and '70s but failed to sound the alarm.

Evidence related to the use of PFAS in oil and gas operations has not been previously publicized. The apparent use of PFAS in these operations adds an especially hazardous class of chemicals to the list of harmful substances associated with oil and gas extraction and is another potential route of exposure to PFAS. In recent years, a growing number of states have set limits on PFAS pollution in water as researchers have discovered hundreds of sites where PFAS from a variety of sources have polluted groundwater. In addition, fire departments are disposing of firefighting foam that contains PFAS. "Fire departments are scrambling to get rid of firefighting foam with PFAS in it because EPA says it's toxic," said Silverio Caggiano, who retired in June 2021 as Battalion Chief with the Youngstown, Ohio Fire Department and is a hazardous materials expert who has trained with fire-fighting foam that contains PFAS. "So if it's too dangerous for us to use, why should oil and gas companies get to use it?"

> "There is evidence from human and animal studies that PFAS exposure may reduce antibody responses to vaccines [citations omitted] and may reduce infectious disease resistance."

Industry records indicating PFAS use in fracking in Arkansas, Louisiana, Oklahoma, New Mexico, Texas, and Wyoming came to light as part of Physicians for Social Responsibility's investigation of the U.S. Environmental Protection Agency's review of three new chemicals proposed in 2010 for use in oil and gas drilling and/or fracking. According to records obtained under a Freedom of Information Act request, EPA regulators worried that the chemicals could break down into products similar to PFOA, the most infamous PFAS, whose use has been largely discontinued in the U.S as part of an agreement between chemical makers and EPA. The regulators were also concerned that the degradation products of the three chemicals could be associated with severe health effects including male reproductive toxicity and tumors.

Despite these concerns, EPA approved the chemicals for commercial use, and EPA records show that one of the chemicals was used commercially for unspecified purposes at least as late as 2018. Records further indicate that the chemical was initially imported for commercial use by Dupont, a company that has agreed to pay hundreds of

EXECUTIVE SUMMARY [CONTINUED]

millions of dollars to settle injury claims related to PFOA pollution. EPA records included only a generic name for the chemical: fluorinated acrylic alkylamino copolymer. More specific identifiers were withheld as trade secrets.

PSR searched for the chemical in FracFocus, a database run by non-governmental organizations where companies operating in more than 20 states disclose well-by-well fracking chemical use. While we did not find the chemical with the name that EPA had approved, we did find other chemicals with related names that had been injected into more than 1,200 wells, the most common of which was "nonionic fluorosurfactant" and various misspellings. Evidence suggests these chemicals are likely PFAS and/or PFAS precursors (substances that could break down into PFAS).

In light of these findings, PSR recommends the following:

- **Health assessment.** EPA and/or states should evaluate through quantitative analysis whether PFAS and/or PFAS breakdown products associated with oil and gas operations have the capacity to harm human health. All potential pathways of exposure should be examined, including inhalation, ingestion, and dermal contact.

- **Testing and tracking**. EPA and/or states should determine where PFAS and chemicals that may be PFAS have been used in oil and gas operations and where related wastes have been deposited. They should test nearby water, soil, flora, and fauna for PFAS.

- **Funding and cleanup.** Oil and gas and chemical firms should be required to provide adequate funding for environmental testing and evaluation, and should PFAS be found, for cleanup. If water cleanup is impossible, the companies responsible for the use of PFAS should pay for alternative sources of drinking water.

- **Public disclosure.** Echoing recommendations by Pennsylvania's Attorney General in 2020, governments should require full public disclosure of drilling and fracking chemicals before each oil or gas well can be developed. EPA and/or states should inform communities potentially exposed to PFAS about PFAS contamination risks so that the communities can take actions such as water testing and treatment.

> "If water cleanup is impossible, the companies responsible for the use of PFAS should pay for alternative sources of drinking water."

- **Moratorium on PFAS use for oil and gas extraction.** Until testing and investigation are complete, EPA and states should not allow PFAS or chemicals that could break down into PFAS to be manufactured, imported, or used for oil and gas drilling or fracking.

- **Limits on drilling and fracking.** The use of PFAS and of chemicals that break down into PFAS in drilling and fracking should prompt governments to prohibit drilling, fracking, and disposal of related wastewater and solid wastes in areas that are relatively unimpacted by oil and gas pollution, and to increase protections in already-impacted regions. When doubt exists as to the existence or danger of contamination, the rule of thumb should be, "First, do no harm."

RECORDS INDICATE PFAS WERE USED IN FRACKING FOR OIL AND GAS

PSR has unearthed evidence suggesting that per- and polyfluoroalkyl substances (PFAS) and/or PFAS precursors (substances that could degrade into PFAS) have been used for hydraulic fracturing ("fracking") in more than 1,200 oil and gas* wells in six U.S. states, creating risks for oil and gas workers and the public through multiple potential pathways of exposure. The lack of full disclosure of chemicals used in oil and gas operations raises the potential that PFAS could have been used even more extensively than records indicate, both geographically and in other stages of the oil and gas extraction process, such as drilling, that precede the underground injections known as fracking. The apparent use of PFAS in oil and gas production has not been previously publicized and raises concerns about toxic exposures.

PFAS are a class of chemicals known for having several valuable properties, including being slippery, oil- and water-repellant, and able to serve as dispersants or foaming agents.[1] The first PFAS to be sold commercially was discovered by a chemist at Dupont and patented as Teflon. Beginning in 1949, it was used in thousands of products, from nonstick cookware to waterproof clothing to plastics to dental floss.[2] Other PFAS have been used in food packaging, fire-fighting foam, and in 3M's widely used fabric protector, Scotchgard.[3] PFAS have been called "perfluorinated chemicals," "polyfluorinated compounds," or PFCs, though the term currently preferred by the U.S. Environmental Protection Agency (EPA) is PFAS.[4] PFAS' nickname "forever chemicals" is rooted in their manufacture, in which hydrocarbon chains of carbon and hydrogen atoms are mixed with hydrofluoric acid. The fluorine atoms in the acid replace the hydrogen atoms in the hydrocarbon chains, forming a bond between fluorine and carbon that is among the strongest in chemistry and barely exists in nature. The result: chemicals that are extremely resistant to breaking down in the environment.[5]

As early as the 1960s and 1970s, researchers inside Dupont and 3M became aware that PFAS were associated with health problems including cancers and birth defects, had accumulated inside virtually every human being, and persisted in the environment.[6] Many of these facts, kept internal by the companies, came to light after attorney Rob Bilott filed lawsuits in 1999 and 2001 against Dupont for causing pollution in and around Parkersburg, West Virginia with PFOA, a type of PFAS used to make Teflon.[7] In December 2011, as part of Dupont's settlement of the 2001 lawsuit, a team of epidemiologists completed a study of the blood of 70,000 West Virginians and found that there was a probable link between PFOA and kidney cancer, testicular cancer, thyroid disease (over- or under-production of hormones by the thyroid gland), high cholesterol, pre-eclampsia (a potentially dangerous complication during pregnancy characterized by high blood pressure and signs of damage to another organ system, most often the liver and kidneys), and ulcerative colitis (a disease causing inflammation and ulcers in the large intestine or colon).[8] Mounting evidence of PFAS's risks has led ten states to develop guidelines for concentrations in drinking water of PFOA and other types of PFAS.[9] One of these states is Michigan, which set standards in 2020 for drinking water and cleaning up groundwater for PFOA and six other forms of PFAS. (The state acted because EPA had not enacted federal drinking water standards for PFAS.) Michigan's maximum allowable level of PFAS is no more than eight parts per trillion for PFOA.[10] By extension, these standards indicate that one measuring cup of PFOA could contaminate almost 8 billion gallons of water, six times the 1.3 billion gallons of water used each day by New York City, or the amount of water needed to fill almost 12,000 Olympic-sized swimming pools at about 660,000 gallons per pool.[11]

PFAS/Fracking Link Began with Investigation of EPA Chemical Approval

PSR found evidence suggesting that PFAS have been used for hydraulic fracturing ("fracking") in the course of an investigation into EPA's approval of chemicals proposed for use in oil and gas drilling and fracking. In fracking, energy companies inject into oil and gas wells a mixture of up to tens of millions of gallons of water, sand, and chemicals at high pressure to fracture underground rock formations,

*Gas, the principal component of which is methane, is also known as "natural" gas, "fossil" gas and "fracked" gas

unlocking trapped oil and gas. The chemicals serve a variety of purposes including killing bacteria inside the wellbore, reducing friction during high-pressure fracking, and as gelling agents to thicken the fluid so that the sand, suspended in the gelled fluid, can travel farther into underground formations.[12]

In 2020, PSR examined documents disclosed by EPA in response to a Freedom of Information Act (FOIA) request that asked EPA to disclose its health reviews and regulatory determinations for new chemicals proposed for use in oil and gas drilling and fracking.[13] We discovered documentation of chemicals proposed to be imported for use in drilling and/or fracking. They were identified by EPA case numbers P-11-0091, P-11-0092, and P-11-0093.[14] And EPA agency regulators worried in writing that these chemicals could degrade into PFOA-like substances.

The relevant documents were created by EPA in accordance with the Toxic Substances Control Act (TSCA), which requires among other provisions that chemical manufacturers or importers submit applications, called "premanufacture notices," in order to receive permission to use new chemicals commercially or to use existing chemicals commercially for new purposes.[15] This system of new-chemicals review is supposed to protect the public from chemical pollution, but it has been heavily criticized over the years as inadequate, including by Congress' investigative arm, the Government Accountability Office (GAO). The GAO has consistently included EPA's program regulating toxic chemicals on its list of federal government programs at highest risk of waste, fraud, abuse, and mismanagement.[16]

Reviewing the EPA's documents was challenging because TSCA allows companies to withhold from the public virtually all the data they submit to EPA in their premanufacture notices. Companies can shield the information from the public by designating it as confidential business information or CBI.[17] In this case, the submitter marked multiple details as CBI, including the chemicals' names, structure, use, production volume, and unique numeric identifiers known as Chemical Abstracts Service (CAS) numbers that scientists consider the best way to identify chemicals.[18] When companies withhold specific chemical identifiers from their premanufacture notices, they must provide a generic or less specific name for their chemical(s) so that the public can have some idea what chemical EPA is assessing.[19] Here, a single generic name was listed for all three chemicals: "fluorinated acrylic alkylamino copolymer."[20] Similarly, manufacturers or importers must list a generic use when the specific use is deemed confidential.[21] Here, the generic use was listed as "oil and water repellent and release agent."[22] Even the company's name was withheld as confidential,[23] leaving the documents riddled with redactions and blank spaces, as may be seen in figures 1 and 2. PSR was, however, able to determine the original submitter's likely identity by digging deeper into EPA data disclosed as required by TSCA.

PMN2010P3

SANITIZED SUBMISSION

PMN Page 3

Part I -- GENERAL INFORMATION						
Section A – SUBMITTER IDENTIFICATION						
Mark (X) the "Confidential" box next to any subsection you claim as confidential						
1a.	**Person Submitting Notice (in U.S.)**					Confidential
Name of Authorized Official	(first) XXX			(last) XXX		
Position	XXX					
Company	XXX					X
Mailing Address (number & street)	XXX					
City	XXX	State		Postal Code	XXX	
email	XXX					
b.	**Agent (if Applicable)**					Confidential
Name of Authorized Official	(first)			(last)		

Figure 1. "Sanitized" premanufacture notice for chemicals with EPA case numbers P-11-0091, P-11-0092, P-11-0093 showing that the chemicals' submitter withheld its own name as confidential. The term "sanitized" means that confidential business information has been withheld from the public version of the document.

Despite the confidentiality, EPA's health and ecological

hazard assessment and consent order regulating the chemicals P-11-0091, P-11-0092, and P-11-0093 show that the agency was concerned about their health and environmental impacts.

The agency's concerns were based in part on the potential that the chemicals might degrade into substances similar to one of the most infamous PFAS in modern chemistry, PFOA.[24] Unfortunately, EPA's assessment and consent order were themselves heavily redacted before being released in response to a FOIA request, preventing a full understanding of EPA's concern. In its consent order, EPA stated:

> EPA is concerned that these perfluorinated degradation products may be released to the environment from incomplete incineration of the PMN [premanufacture notice] substances at low temperatures. EPA has preliminary evidence, including data on other [REDACTED], that suggests that, under some conditions, the PMN substances could degrade in the environment. EPA has concerns that these degradation products will persist in the environment, could bioaccumulate or biomagnify, and could be toxic (PBT) to people, wild mammals, and birds based on data on analog chemicals, including PFOA and [REDACTED]. The presumed perfluorinated degradants for these PMN substances include [REDACTED].[25]

PMN2010P5A

SANITIZED SUBMISSION

PMN Page 5a

c. Please identify which method you used to develop or obtain the specified chemical identity information reported in this notice (check one).				CBI
Method 1 (CAS Inventory Expert Service - a copy of the identification report obtained from CAS Inventory Expert Service must be submitted as an attachment to this notice)	X	IES Order Number	152725-1	**Method 2** (other source) ☐
Enter Attachment filename for Part I, Section B, 2. c.		CAS - Inventory Expert Service (2010) #1 (public).pdf		☐
d. The currently correct Chemical Abstracts (CA) name for the polymer that is consistent with TSCA Inventory listings for similar polymers.				X
XXX				
CAS Registry Number (if a number already exists for the substance)		XXX		

Figure 2. "Sanitized" premanufacture notice for chemicals with EPA case numbers P-11-0091, P-11-0092, P-11-0093 showing that the chemicals' submitter withheld the chemicals' Chemical Abstracts Service registry numbers – the surest identifier for a chemical's identity – as confidential.

The acronym PBT stands for (P) persistent, (B) bioaccumulative, and (T) toxic.[26] EPA did not answer a question sent via email by PSR about the circumstances in which the substances described in the premanufacture notice might be incompletely incinerated.

In discussing PFOA, to which EPA regulators had likened the degradation products of the three chemicals, the regulators added that

> toxicity studies on PFOA indicate developmental, reproductive and systemic toxicity in various species. Cancer may also be of concern. These factors, taken together, raise concerns for potential adverse chronic effects in humans and wildlife."[27]

EPA also expressed significant health concerns in its health and ecological hazard assessment. The agency wrote:

> For the potential incomplete incineration/environmental degradation product, based on the test data for the analogue [REDACTED], concerns are liver toxicity, blood toxicity, and male reproductive toxicity....There is also

concern for immunosuppression and oncogenicity based on data for [REDACTED].[28]

On November 29, 2011, the undisclosed company that had requested the approval of the three new chemicals began importing one of the chemicals for commercial use, the one known by EPA case number P-11-0091, according to a document filed with EPA.[29] (The related chemicals, P-11-0092 and P-11-0093, have not been used commercially.[30]) An additional EPA record shows that chemical P-11-0091 may have been used in oil and gas wells, among other uses, at least as recently as 2018.[31]

Search of Fracking Database Indicates Use of PFAS in Oil and Gas Operations

To determine if the chemical known as P-11-0091 had been used in oil and gas operations, PSR searched for "fluorinated acrylic alkylamino copolymer," the chemical's generic name, in a publicly available online database of well-by-well fracking chemical disclosure maintained by FracFocus, a nongovernmental organization run by the Groundwater Protection Council and the Interstate Oil and Gas Compact Commission. The database, which began operating in 2011, contains records on the hydraulic fracturing chemicals used in thousands of wells across the nation. Twenty-five states require or allow reporting of hydraulic fracturing chemicals to the database.[32] Companies in states in which reporting to FracFocus is not required can, and sometimes do, report hydraulic fracturing chemical use voluntarily to FracFocus. The database can be searched for chemicals used across multiple wells.[33]

While PSR did not find any uses of "fluorinated acrylic alkylamino copolymer," we did find chemicals with related names had been used to fracture more than 1,200 wells primarily in Texas but also in Arkansas, Louisiana, Oklahoma, New Mexico, and Wyoming between 2012 and 2020. The most frequent use occurred prior to 2016. Chemicals with related names included:

- fluorinated benzoic salts
- Fluoroalkyl Alcohol Substituted Polyethylene Glycol
- fluoro surfactants – proprietary
- meta-Perfluorodimethylcyclohexane
- Perfluoro-1,3-dimethylcyclohexane
- nonionic fluorosurfactant (and multiple misspellings of the same term)

A variety of evidence shows that these chemicals are or could be PFAS and/or PFAS precursors. EPA lists two of the chemicals, meta-Perfluorodimethylcyclohexane and Perfluoro-1,3-dimethylcyclohexane, in the agency's "Master List of PFAS Substances."[34] According to two chemical experts, both of whom are authors of multiple peer-reviewed articles about chemicals related to oil and gas production,[35] all of the chemicals are PFAS or could degrade into PFAS. The two experts are Zacariah Hildenbrand, a research professor in Chemistry and Biochemistry at the University of Texas at El Paso, and Kevin Schug, Shimadzu Distinguished Professor of Analytical Chemistry at the University of Texas at Arlington.[36] In addition, Wilma Subra, who has a master's degree in chemistry and is a recipient of a John D. and Catherine T. MacArthur Foundation "Genius" Grant for her work helping to protect communities from toxic pollution, identified all of the chemicals as potentially PFAS. Subra, based in Louisiana, has spent decades working to reduce and remediate pollution from oil and gas operations.[37] And yet another expert, Linda Birnbaum, a board-certified toxicologist and former director of the National Institute of Environmental Health Sciences, informed PSR that all of the chemicals are likely to be PFAS.[38]

Are any of these chemicals in the FracFocus database the "fluorinated acrylic alkylamino copolymer" approved by EPA? Each of the four chemical and health experts said that was a possibility. However, it is impossible to know conclusively without having the precise identifier, known as a CAS number, both for the EPA-approved chemical and for the chemicals listed in the FracFocus records. CAS numbers are unique numeric identifiers assigned to each chemical by the American Chemical Society. They are the most accurate way

to identify chemicals, because a chemical can have multiple names or trade names but only one CAS number.[39]

Major Oil and Gas Companies Likely Used PFAS and/or PFAS Precursors

According to the publicly available data in the FracFocus database, more than 130 oil and gas companies reported using the chemicals that, according to experts and EPA's list of PFAS substances, are or could be PFAS and/or PFAS precursors. These companies include some of the most prominent producers of oil and gas. Among them:

- XTO Energy Inc., a subsidiary of ExxonMobil, one of the world's largest oil and gas producers, disclosed using one of the chemicals, nonionic fluorosurfactant, in 78 wells in New Mexico, Oklahoma, and Texas between 2013 and 2019.

- Chevron Corp., another major producer, reported using nonionic fluorosurfactant in 38 wells in New Mexico and Texas in 2013 through 2015.

- Anadarko Petroleum Corp., reported using nonionic fluorosurfactant in eight wells in Texas in 2013-2014. Anadarko was the co-owner, along with BP, of the Macondo well that spewed millions of gallons of oil into the Gulf of Mexico in 2010.[40]

- EOG Resources, Inc., one of the largest oil producers from shale deposits in the U.S.,[41] reported using fluoroalkyl alcohol substituted polyethylene glycol in 99 wells in New Mexico and Texas from 2012-2014 as well as nonionic fluorosurfactant in one well in Texas in 2014.

- Encana Corp., once one of Canada's largest oil companies, disclosed the use of nonionic fluorosurfactant in four wells in Texas in 2014-2015. Encana moved its corporate headquarters to the U.S. in 2020 and changed its name to Ovintiv.[42]

The table below shows a sampling of wells fractured by these five companies and the estimated maximum amount, in pounds, of chemicals that may be PFAS used in each well.

Each chemical in the table comprises a tiny percentage of the total amount of hydraulic fracturing fluid injected into each well – in one case as small as 0.00016 percent of the total.[44] However, because oil and gas companies can inject millions of gallons of hydraulic fracturing fluid into each of their wells, small percentages can add up to hundreds of pounds of chemicals or more. When chemicals are as

Examples of Apparent PFAS Chemicals and/or PFAS Precursors Utilized in Hydraulic Fracturing

Company	Well Number	State	County	Year	Potential PFAS Used in Well	Estimated Maximum Amount (lbs)
XTOEnergy/ExxonMobil	35-019-26303	OK	Carter	2019	Nonionic Fluorosufactant	17.60
XTOEnergy/ExxonMobil	35-019-26301	OK	Carter	2019	Nonionic Fluorosufactant	27.41
Encana (Ovintiv)	42-461-39585	TX	Upton	2015	Nonionic Fluorosurfactant	31.98
EOG Resources, Inc.	30-025-42387	NM	Lea	2015	fluoroalkyl alcohol substituted polyethylene glycol	114.63
EOG Resources, Inc.	30-025-42386	NM	Lea	2015	fluoroalkyl alcohol substituted polyethylene glycol	120.07
Encana (Ovintiv)/Athlon	42-173-36707	TX	Glasscock	2014	Nonionic Fluorosurfactant	324.87
Chevron	42-105-36572	TX	Crockett	2014	Nonionic Fluorosurfactant	25.25
Chevron	42-105-39233	TX	Crockett	2014	Nonionic Fluorosurfactant	23.23
Anadarko	42-105-40668	TX	Crockett	2013	Nonionic Fluorosurfactant	108.10
Anadarko	42-105-40818	TX	Crockett	2013	Nonionic Fluorosurfactant	8.94

Table 1. The estimated maximum amount of chemicals that may be PFAS, in pounds, used by five different oil and gas companies to hydraulically fracture selected wells in New Mexico, Oklahoma and Texas between 2013 and 2019. For a detailed explanation of the calculations in the table, see the endnote.[43]

toxic as PFAS can be, even small quantities could cause extensive contamination through multiple pathways. "There's a potential for [PFAS] to contaminate a huge amount of water or soil or sediment if it were to spill on the surface," said chemist Subra in a telephone interview, noting that the amounts of potential PFAS in the table could pose a risk. "It doesn't take much to be present in those media to be a threat to health."[45]

In most cases, the declared uses of the chemicals in FracFocus were not much more specific than the generic name offered. Hundreds of uses were listed as some type of surfactant, including "fluoro surfactant" and "water recovery surfactant."[46] According to EPA:

> surfactants are substances that lower the surface tension of a liquid, the interaction at the surface between two liquids (called interfacial tension), or that between a liquid and a solid. Surfactants may act as detergents, soaps, wetting agents, degreasers, emulsifiers, foaming agents and dispersants.[47]

FracFocus also reflected a handful of other uses, including the use of "meta-Perfluorodimethylcyclohexane" as a tracer. It was injected in four wells in Sublette County, Wyoming in 2015 and 2016.[48] Tracers are used to help oil and gas companies infer information about underground formations.[49] EPA documents disclosed in November 2020 show that PFAS have been proposed for use as tracers.[50]

PFAS May Have Been Used for Decades in Oil and Gas Operations

Two sources suggest that the use of PFAS in oil and gas operations dates back decades and involves the use of the chemicals in a range of extraction techniques. The authors of a paper published in 2020 in the peer-reviewed journal *Environmental Science: Processes and Impacts* found that more than 50 PFAS have been used or proposed to be used to extract oil and gas, based on public records dating to 1956 that include patents, journal articles, and databases. The authors cautioned that they were not able to verify the information they found, but the records indicate that PFAS have been used to extend underground fractures, to increase the permeability of underground formations, to make the surfaces of underground oil-bearing reservoirs water- and oil-resistant, and as foaming agents.[51]

In a 2008 paper in *The Open Petroleum Engineering Journal*, two authors, including at least one from Dupont, wrote that:

> while fluorosurfactants have been used in gas and oil exploration for four decades, the increased demand for petroleum and the greater understanding of the benefits of fluorosurfactants have led to growing acceptance for fluorosurfactants throughout the petroleum industry.[52]

The authors did not explicitly say that fluorosurfactants were PFAS, but they wrote that "the use of fluorosurfactants is a recent but growing trend due to (i) the exceptional hydrophobic and oleophobic nature of the perfluoroalkyl and perfluoroalkyl ether groups…"[53] Thus, at least some of the fluorosurfactants mentioned in the article appear to be PFAS. Furthermore, the article indicated that use of fluorosurfactants was growing and, referring to them as an "emerging technology," said that fluorosurfactants showed promise in a variety of extraction techniques including fracking, drilling, and waterflooding.[54] Like the authors in the 2020 paper in *Environmental Science: Processes and Impacts*, the authors noted that they relied mostly on patents and laboratory models "vs actual oil and gas recovery experiments."[55]

OIL AND GAS CHEMICALS CAN POSE SERIOUS HEALTH RISKS

Shedding light on the use or possible use of PFAS in oil and gas extraction is important because, for years, people living near oil and gas operations have experienced contaminated water and serious illnesses that they believe are related to the chemicals associated with these activities.[56] During the 2000s, these concerns intensified as oil and gas companies moved into more heavily populated areas to drill so-called unconventional formations such as coalbed methane and shale.[57] To reach the new deposits, the companies have used hydraulic fracturing, often combined with horizontal drilling.[58]

As previously discussed, chemicals are injected into oil and gas wells as an integral part of the fracking process. They are also used during drilling, which precedes fracking. During drilling, companies bore deep holes in the earth; these holes typically pass directly through groundwater. Chemicals can be injected in this stage of the process to help keep the drill bit cool and to lift rock cuttings out of the well,[59] and at this point in the process, no protective structures are in place to keep those chemicals from entering groundwater. Following drilling and fracking, a portion of the water, sand and chemicals injected into oil and gas wells during fracking, as well as naturally occurring contaminants such as carcinogenic benzene[60] and radium,[61] flow out of the well in the form of wastewater.[62] Wastewater can reach volumes of millions of gallons per well.[63]

Use of PFAS in oil and gas operations would add a highly potent substance to an already long list of toxic chemicals associated with oil and gas extraction. In 2016, EPA published a study of fracking and drinking water that identified 1,606 chemicals used in fracking fluid and/or found in wastewater. While the agency found high-quality information on health effects for only 173 of these chemicals, that information was troubling. EPA found that "health effects associated with chronic oral exposure to these chemicals include carcinogenicity [for both benzene and radium], neurotoxicity, immune system effects, changes in body weight, changes in blood chemistry, liver and kidney toxicity, and reproductive and developmental toxicity."[64] Chemicals used in the drilling stage can also pose health risks, including developmental toxicity and the formation of tumors, according to EPA regulators.[65] A disclosure form filed with the state of Ohio, perhaps the only state to require disclosure of drilling chemicals, shows that Statoil, Norway's state oil company since renamed Equinor, has used neurotoxic xylene in drilling.[66]

The lack of high-quality health testing data for the other 1,400-odd chemicals identified by EPA does not necessarily mean that they are safe; it might simply mean that they have not been adequately tested. The federal Toxic Substances Control Act (TSCA) has likely contributed to these gaps because it has not required health testing for new chemicals. According to Congress' investigative arm, the Government Accountability Office, chemical manufacturers have often avoided such testing, and EPA often has not asked for it despite having the authority to do so.[67] Congress updated TSCA in 2016 to strengthen EPA's authority to ask for health testing,[68] but according to the Environmental Defense Fund, the Trump administration EPA failed to use this improved authority.[69] Separately, EPA noted that its list of chemicals associated with fracking was likely incomplete because chemical manufacturers treat many chemicals used in oil and gas drilling as trade secrets, as permitted by TSCA.[70]

A new health concern related to PFAS and its use or possible use in oil and gas operations is that the chemicals could compromise the effectiveness of vaccines for COVID-19. The U.S. Centers for Disease Control and the Agency for Toxic Substances and Disease Registry issued the following statement in June 2020:

> CDC/ATSDR understands that many of the communities we are engaged with are concerned about how PFAS exposure may affect their risk of COVID-19 infection. We agree that this is an important question....CDC/ATSDR recognizes that exposure to high levels of PFAS may impact the immune system. There is evidence from human and animal studies that PFAS exposure may reduce antibody responses to vaccines [citations omitted], and may reduce infectious disease resistance [citation omitted]. Because COVID-19 is a new public health concern, there is still much we don't know. More

HEALTH RISKS [CONTINUED]

Figure 3 shows an example of a spill of fracking fluids. The photo is from the U.S. Environmental Protection Agency and shows a fire on June 28-29, 2014 at the Eisenbarth Well operated by Statoil (since renamed Equinor) in Monroe County, Ohio. The photographer is not listed.[74] According to an EPA report, trade secret fracking chemicals along with other chemicals were spilled because of the fire. Fluids that may have contained the trade secret chemicals ran off the well pad into a tributary of the Ohio River. An estimated 70,000 fish died.[75]

research is needed to understand how PFAS exposure may affect illness from COVID-19.[71]

Multiple Potential Pathways to Human Exposure

EPA and others have identified multiple pathways through which people could be exposed to the chemicals associated with oil and gas extraction including, potentially, PFAS. The agency indicated that any chemicals used during the first stage of the drilling process would be highly likely to leach into groundwater because during this stage, drilling passes directly through groundwater zones[72] before any casing or cement is placed in the well to seal it off from surrounding aquifers.

EPA found that during the fracking phase that follows drilling, exposure pathways could include:

- spills of fracking fluid that seep into groundwater;
- injection of fracking fluid into wells with cracks in the casing or cement, allowing the fluid to migrate into aquifers (much of the fracking fluid can remain underground);

- injection of fracking fluids directly into groundwater;
- underground migration of fracking fluids through fracking-related or natural fractures;
- intersection of fracking fluid with nearby oil and gas wells, and
- spills of wastewater after the fracking process is completed, and inadequate treatment and discharge of fracking wastewater to surface water supplies.[73]

Additional potential pathways of concern involve wastewater. These include intentional dumping of fracking wastewater into waterways,[76] spreading wastewater on roads to suppress dust or melt snow and ice,[77] and the use of wastewater for irrigation of agricultural crops.[78] In addition to these intentional uses, underground leaks can occur from underground injection wells into which well operators have pumped billions of gallons of drilling and fracking wastewater for disposal.[79] This injected wastewater is intended to remain in underground formations permanently but has been known to leak and pollute groundwater.[80] In addition, drilling and fracking chemicals can become airborne at oil and gas sites through various routes[81] including by volatilizing from huge ground-level pools of wastewater[82] or from tanks that store condensate, a naturally-occurring liquid associated with gas.[83]

The toxic and secret chemicals used in drilling and fracking can also pose a risk not only to people living near oil and gas production wells in relatively rural areas but also to people living near wastewater disposal sites, especially underground injection wells;[84] in densely populated areas with oil and gas drilling, such as Los Angeles;[85] and in urban areas downstream from fracking or wastewater disposal activity.[86] In 2019, New Jersey governor Philip D. Murphy called for a ban on fracking and the disposal of fracking wastewater in the Delaware River Basin, a multi-state watershed that provides drinking water for more than 13 million people and encompasses parts of Pennsylvania that could be drilled for gas.[87] "As noted by the Environmental Protection Agency in its 2016 report on the impact of fracking on water resources," Murphy wrote:

> the ability of regulatory agencies to assess the full impacts of fracking wastes on public health and the environment is hampered by the prevalence of confidentiality claims that prevent disclosure of the chemical constituents of fracking fluids…Therefore, prohibiting all fracking activity in the Basin is vital to avoid injury and preserve the waters of the Basin and protect public health.[88]

In February 2021, the Delaware River Basin Commission, of which Murphy is a member, banned fracking in the Basin, citing in part the risks of chemicals associated with the process.[89] The decision made permanent a de facto moratorium on fracking that the commission had maintained for more than 10 years.[90] The commission said that by September 30, 2021 it would propose amendments to its rules regarding the importation of fracking wastewater into the basin and export of freshwater from the Basin.[91]

Evidence of Harm to Human Health from Oil and Gas Operations

Residents living near oil and gas operations have increasingly reported illnesses that they believe are related to chemical exposures, while expressing frustration about the secrecy surrounding many of the chemicals used by the oil and gas industry.[92] In 2020, Pennsylvania's Attorney General issued a report based on a criminal grand jury investigation of oil and gas drilling pollution in the Keystone State, where drilling for gas in shale formations has surged over the past 15 years.[93] That surge has vaulted Pennsylvania into the number two spot among gas-producing states (Texas is number one)[94] and brought thousands of Pennsylvanians into contact with gas drilling and its impacts. Based on testimony from over 70 households, the attorney general found that

> Many of those living in close proximity to a well pad began to become chronically, and inexplicably, sick. Pets died; farm animals that lived outside started miscarrying, or giving birth to deformed offspring. But the worst

> was the children, who were most susceptible to the effects. Families went to their doctors for answers, but the doctors didn't know what to do. The unconventional oil and gas companies would not even identify the chemicals they were using, so that they could be studied; the companies said the compounds were "trade secrets" and "proprietary information." The absence of information created roadblocks to effective medical treatment. One family was told that doctors would discuss their hypotheses, but only if the information never left the room.[95]

In addition to these and other self-reported or anecdotal reports, peer-reviewed studies of people living near oil and gas operations provide scientific evidence of illnesses and other health effects. A 2019 study in the journal *Environment International* examined 3,324 babies born in Colorado between 2005 and 2011 and found that, compared with control groups, congenital heart defects were 1.4 and 1.7 times more likely in babies born to mothers in areas of medium and high unconventional gas drilling, respectively.[96] A 2018 study in the *Journal of Health Economics* found that babies born between 2003 and 2010 to Pennsylvania mothers living near a functioning shale gas well had a higher incidence of low birth weight compared to babies born of mothers living near a permitted well that had not yet gone into production.[97] Low birthweight is a leading contributor to infant death in the United States.[98] A 2017 study in *PLOS One* of Coloradans between birth and 24 years old diagnosed with cancer between 2000 and 2013 found that those between the ages of five and 24 were more than four times more likely to live in areas of heavy oil and gas drilling, compared to controls.[99] In 2019, Pennsylvania-based FracTracker Alliance conducted a meta-analysis of 142 health studies published between 2016 and 2018 focusing on health impacts of unconventional oil and gas development (UOGD). The analysis concluded, "The results of this study indicate that a variety of health impacts in every major organ system are being experienced by individuals living near UOGD." Specific health effects included cancer, early infant mortality, pre-term birth, and poor infant health.[100] The Southwest Pennsylvania Environmental Health Project,[101] and PSR and the Concerned Health Professionals of New York,[102] have likewise compiled the substantial and growing number of scientific studies that have found serious health effects associated with oil and gas drilling.

Disadvantaged Communities Bear Disproportionate Oil and Gas Exposure Risks

"Fenceline" communities – people living adjacent or close to oil and gas operations – often bear a disproportionate risk of exposure to drilling and fracking chemicals. And although drilling and fracking take place in the majority of U.S. states, not everyone shares in that risk equally. Rather, oil and gas infrastructure and associated chemicals are frequently located in or adjacent to poor, underserved, and marginalized communities, indigenous communities, and communities of color.[103] For example, a 2019 analysis conducted in Colorado, Oklahoma, Pennsylvania, and Texas found strong evidence that minorities, especially African Americans, disproportionately lived near fracking wells.[104] A separate study focusing on West Virginia, Ohio, and Pennsylvania found that in Pennsylvania, a higher concentration of unconventional gas wells are located in lower-income communities, and that localized clusters of vulnerable populations are exposed to high levels of well density in all three states.[105] A study of census tract data in western Pennsylvania shows that among nearly 800 gas wells, only two were drilled in communities where home values exceeded $200,000.[106] And a study published in 2018 found that oil and gas wastewater injection wells in Ohio were disproportionately located in rural, lower-income areas.[107]

Various population sectors are more vulnerable than others to harm from chemical exposure. This includes pregnant women; the young, whose vital organs are still in development; people with preexisting medical conditions; the elderly; and those who live where pollutants from multiple sources combine to create a high cumulative load of toxic exposures.[108] Where vulnerable populations also have limited access to health care, their health risks are magnified. In short, the health disparities that already exist in U.S. society combine with proximity to oil and gas operations to impose a disproportionate health burden on the poorest, the

sickest, the young, the elderly, and people of color.

Also at high risk are oil and gas field workers and waste handlers and first responders. Industry workers who may handle or otherwise be exposed to fracking-related chemicals may not have the personal protective equipment needed to shield them from exposure, much less the training necessary to take protective or remedial measures.[109] The same is true for first responders called to an emergency at a site of oil and gas operations. Confidential business information or trade secret claims may hide from them the identity and effects of the chemicals they may be exposed to, leaving them unable to determine how potentially dangerous chemicals should be handled or contained.[110]

Other Experts Voice Concern about Exposure to PFOA-like Substances

The possibility that people could be unknowingly exposed to PFAS in oil and gas extraction is of concern to other specialists, including experts in toxic exposure and other scientists. Toxicologist David Brown, who has investigated health effects associated with unconventional gas drilling with the Southwest Pennsylvania Environmental Health Project, has suggested two likely pathways to human exposure for PFAS chemicals that could occur in oil and gas extraction: 1) through air, when gas is burned off during flaring, or 2) through the use of contaminated groundwater for bathing, cooking, drinking or washing laundry, which would allow chemicals in the water to be ingested or to be inhaled if the chemicals were to volatilize (evaporate or disperse as a gas) inside the home. "Anything injected down the well will come back up," said Brown, who also served on a panel that advised the state of Massachusetts Department of Environmental Protection Office of Research and Standards on development of drinking water standards for PFAS. "People will get exposed." He added that the risks could be significant. "PFAS compounds are sequestered in the body for long periods after ingestion, leading to long-term but undefined health risks. Individuals and communities need to be aware of the presence of such chemicals so that they can take protective action."[111]

Silverio Caggiano, who retired in June 2021 as Battalion Chief and hazardous materials expert with the Youngstown, Ohio Fire Department, expressed dismay that the federal government and state governments would act to protect firefighters and the public from PFAS in some ways, but leave them at risk in other ways. He noted that both EPA and the U.S. Fire Administration, a division of the Federal Emergency Management Agency, have issued warnings and initiatives to discontinue the use of old Aqueous Film Forming Foam (AFFF), used to fight fires for years, and to dispose of it properly because it can contain PFAS.[112] Yet at the same time, government agencies have failed to acknowledge the potential use of PFAS in association with oil and gas wells. "Fire departments around the country are scrambling to extract any of this older AFFF from their inventories," he said,

> yet when firefighters and first responders are called to a frac well incident, the governments both state and federal act as if this chemical danger doesn't exist on-site. It makes one wonder who the EPA would cite for contamination if a fire department used old PFAS-containing AFFF to put out a well fire that had PFOA-style chemicals on-site. These games have to end. The jobs of firefighters are dangerous enough without the continuous shell game the chemical industry and regulators play with toxic chemicals.[113]

Robert Delaney, a geologist who until his retirement in November 2020 led an initiative for the Michigan PFAS Action Response Team to address contamination of PFAS at U.S. Department of Defense sites in the state, said that communities should be very concerned about the use of PFAS in oil and gas drilling. Delaney spent 36 years working in natural resource protection for the state of Michigan and first warned state officials about the looming problem with PFAS in 2012, though unrelated to oil and gas extraction.[114] PFAS, he said,

> disperses all over, it doesn't break down, and the levels at which it is dangerous are so, so low. It becomes an enormous problem. I call it a nightmare contaminant. I used to think that benzene, TCE (trichloroethylene), polyvinyl chloride were the really nasty ones to deal with, and then I saw these.[115]

HEALTH RISKS [CONTINUED]

Delaney also noted that cleaning up water contaminated with PFAS is expensive if any significant volume is involved, because the water must be run through activated carbon, the same material in Brita filters. The amount of activated carbon needed would be vast and could cost millions of dollars, as it has in the ongoing effort to remove PFAS from drinking water at Michigan's Wurtsmith Airforce Base. And after the activated carbon fills up with PFAS and any additional contaminants in the water, it must be disposed of somewhere. "Part of the problem is landfills won't take it because they don't know how much liability they're taking on" if PFAS waste were to contaminate the landfill, Delaney observed.

As of 2020, Michigan was trying to clean up groundwater at 137 sites that exceed its new standards for PFAS pollution. "There are a lot of sites in Michigan because we are looking," Liesl Clark, director of the Michigan Department of Environment, Great Lakes and Energy told the Detroit Free Press. "If other states were doing the same sorts of work, they would be finding a similar challenge — and some states are."[116]

Carol Kwiatkowski, former Executive Director of The Endocrine Disruption Exchange, the first organization to catalogue the health effects of chemicals used in oil and gas drilling and fracking, said in an email to PSR that

> current efforts to address the problem of PFAS contamination focus on waste incineration or filtering of drinking water. Neither process is 100% effective, nor do they clean up the PFAS that have polluted large river systems or the air. In other words, there is no effective way to remove them.

Kwiatkowski, who is currently Science and Policy Senior Associate at the Green Science Policy Institute, added that "the most effective solution is to stop their use and production as quickly as possible, except for uses where they are absolutely necessary, for example in medical equipment."[117] PSR concurs.

EPA OK'D PFAS-RELATED CHEMICALS FOR OIL AND GAS DESPITE RISKS

For years, attorney Bilott, environmentalists, and even the state government of Michigan have raised concerns that EPA was not adequately protecting the public from PFAS pollution.[118] EPA's approval of three chemicals for use in oil and gas operations that regulators believed could degrade into PFOA-like substances raises additional concerns about the agency's commitment to protecting people and the environment from dangerous substances.

By the time EPA regulators reviewed the chemicals P-11-0091, P-11-0092, and P-11-0093 in 2010, the agency would have had a firm basis for concern about chemicals that could degrade into PFOA-like substances. It was already well-known that PFOA and PFOS (used to make Scotchgard) were extremely harmful. In 2004, Dupont had settled Bilott's lawsuit alleging PFOA-related harm for $70 million, plus promises to pay for water filtration and the scientific study that in 2011 found serious health impacts related to PFOA.[119] In 2005, EPA reached a then-record $16.5 million settlement with Dupont after accusing the company of violating TSCA by failing to disclose information about PFOA's toxicity and presence in the environment.[120] In 2006, EPA invited Dupont, 3M and six other companies to join a "stewardship" program in which the companies promised to achieve a 95 percent reduction of emissions of PFOA and related chemicals by 2010, compared to a year 2000 baseline. The agreement also required the companies to phase out manufacture and use of PFOA by 2015.[121] In 2021, EPA says on its website that the companies reported that they had accomplished the goals either by exiting the PFAS industry or by transitioning to alternative chemicals.

Manufacture and importation of PFOA itself has ceased, though there could still be some PFOA use from existing stocks, and it could be contained in imported items.[122] However, since the announcement of its PFAS stewardship program in 2006, EPA has allowed multiple new PFAS to be used commercially.[123] And in 2015, a group of more than 200 scientists raised health and environmental concerns that the new short-chain PFAS designed to replace PFOA and PFOS may not be safer for health or the environment.[124] These "replacement" substances may include the parent chemical or the breakdown products discussed in this report.

Dupont Was the Likely Importer of Chemical P-11-0091

Beyond the health risks of PFOA, EPA should have been troubled by the likely importer of the new chemicals proposed for use in oil and gas operations: Wilmington, Delaware-based Dupont. This tentative identification is based on the EPA-issued "accession number" that was issued for the chemical P-11-0091 that went into commercial use. When EPA receives a notice (called a "notice of commencement") that a chemical is going to be imported or manufactured for commercial use and the chemical's identity is hidden from the public as confidential business information, the agency assigns the chemical an accession number. This number allows the public to find the chemical on the TSCA inventory, a list of existing chemicals in commerce, without learning the chemical's specific identity.[125] The accession number also allows the public to search for data about the chemical submitted by chemical manufacturers and importers every four years under TSCA's Chemical Data Reporting rule. These data provide EPA and the public with some information about the use of chemicals in commerce in each of the four years preceding the submission year.[126]

Using the accession number – 277420 – that was issued to chemical P-11-0091, PSR searched online data filed in 2016 that provided information on use of this chemical during each of the years 2012 through 2015. The company listed as having imported or manufactured the chemical from 2012 through 2015 was Wilmington, Delaware-based Chemours. There was, however, a puzzling discrepancy: The Chemours company did not exist until July 1, 2015, when it was created by Dupont as a spinoff company that would manufacture "performance chemicals."[127] Under that timeline, Chemours could not have been reporting on its own chemicals until the second half of 2015. What company, then, was manufacturing or importing the chemical from 2012 until mid-2015?

We believe there is an explanation to be found under EPA reporting guidance. The guidance provides that when a manufacturing division of a company is separated from

a parent company to become an independent entity, yet continues to manufacture or import the same substances it did previously, it retains the responsibility for reporting the manufacture or importation of those substances over a four-year reporting period, including the manufacturing or importing that it did while a unit of the parent company.[128] According to at least two different articles in a chemical industry trade publication, Chemours took over what used to be Dupont's performance chemical business – one that included fluorochemicals,[129] a class that would encompass the chemical with case number P-11-0091 and/or its PFOA-like breakdown products. As the successor of the division of Dupont that manufactured or imported fluorochemicals, Chemours in 2016 would have had a duty under EPA's guidance to report fluorochemicals under its own name that were previously made or imported by Dupont in 2012, 2013, 2014, and for the first half of 2015. The chemical with case number P-11-0091 and accession number 277420 apparently qualified as one of these chemicals.

An alternate explanation could be that Chemours was reporting a chemical previously made by or imported by a company other than Dupont that had merged with, or been acquired by, Chemours. In this scenario, EPA's guidance states that if the other company had ceased to exist following the merger or acquisition, Chemours would have had the duty to report on behalf of the previously separate company.[130] However, Chemours' Form 10-K filed with the U.S. Securities and Exchange Commission in 2016 does not reflect any mergers and acquisitions involving Chemours in the first half-year of its existence (the second half of 2015).[131] It is therefore likely that it was Dupont and not some other company that originally sent notice to EPA in November 2011 that it was importing chemical P-11-0091. It is also likely that Dupont continued to import or manufacture the chemical through at least July 2015, when Chemours became a separate company.[132] In February 2021, PSR wrote to Dupont via FedEx delivery service and to Chemours via certified U.S. mail, sharing details of our investigation and asking the companies, among other things, whether Dupont was the original importer of chemical P-11-0091. PSR did not receive a response from either company.)

The likely scenario that Dupont originally imported and/or manufactured the chemical P-11-0091 should concern the public because Dupont has a history of harming people and polluting the environment with PFOA while withholding knowledge of PFOA's risks.[133] As is discussed above, the company in the past failed to communicate to the public the risks of PFOA, and widespread pollution occurred before people and regulators could act to protect themselves. PSR is concerned that a similar result could occur with chemical P-11-0091.

Dupont's likely involvement with chemical P-11-0091, and Chemours' documented involvement, also raise concerns about significant financial damages. In creating Chemours as a separate company, Dupont made Chemours responsible for hundreds of millions of dollars of what was previously Dupont's liability related to PFOA.[134] In 2019, Chemours sued its own parent company, alleging that Dupont had understated how much liability Chemours would be responsible for. Chemours has already paid hundreds of millions of dollars to settle PFOA-related damage claims against Dupont,[135] and Dupont itself has agreed to pay hundreds of millions of dollars to settle such claims. Could significant financial damages be associated with chemical P-11-0091 as well?

EPA Regulation of the Chemical Was Lax

One fact is clear: EPA's regulation of chemical P-11-0091 and the two related chemicals that did not go into commercial use was lax. Despite the agency's own finding that these chemicals could break down into PFOA-like substances, EPA did not issue any requirement that follow-up testing be performed to see if the breakdown of the chemicals took place. Neither did the agency call for tracking to determine where the chemicals were being used, or if these substances were contaminating the environment as the agency had feared. Nor did it require that use of the chemicals be prohibited within a certain distance of drinking water sources, homes, or schools.

EPA told the nonprofit organization Partnership for Policy Integrity in 2016 that it does not track where new chemicals are used when they are reviewed and regulated under TSCA and lacked the staff to test for the new chemicals near water supplies.[136] PSR asked EPA whether the agency

tracked where chemical P-11-0091 was used, but EPA did not respond. Indeed, there are no regulations or statutes that systematically require EPA to report the locations where a chemical is used after it is approved for commercial use. The chemical data reporting system requires reporting in some cases of the location of facilities where chemicals are manufactured or imported, but not the locations of end uses.[137] There is no indication that EPA tracked the end uses of chemical P-11-0091. In its consent order, EPA did require the importer to conduct certain tests if the company reached certain production volume or importation thresholds. (These thresholds were redacted.) EPA also required the importer to limit impurities in the chemicals to certain levels, provide EPA yearly reports on impurities in the chemicals, and maintain certain records.[138] EPA also said that the company would "annually analyze the starting material, [REDACTED] for perfluorooctanoic acid (PFOA)."[139]

EPA's Decision to Approve Chemicals May Have Relied on Dubious Assumptions

Why did EPA approve the chemicals P-11-0091, P-11-0092, and P-11-0093 for commercial use despite its health concerns? The agency offered no explicit reason, but one indication appears in the consent order the agency issued in 2011: EPA wrote that it believed, based on testing data for redacted substances, that the three chemicals would be less likely than PFOA to bioaccumulate in people.[140]

EPA also said that testing data on redacted substances "indicate a different and less toxic profile for [REDACTED] (a presumed environmental degradant of the PMN substances) than for PFOA."[141] It is unclear whether the agency was correct, but without careful testing, there is no guarantee that newer chemicals will be safer than the toxic chemicals they replace. The Chicago Tribune has investigated the use of flame retardants, for example, and has found that after toxic flame retardants such as PCBs and PBBs were replaced in the 1970s by substitute chemicals such as PBDEs, the replacement chemicals were found to have toxic problems of their own. Some of these replacements are now being phased out – in favor of yet another generation of flame retardants that have also been associated with health problems.[142]

Even after suggesting that the new chemicals were less of a health and environmental risk than PFOA, EPA expressed misgivings about approving the substances for commercial use. EPA wrote:

> However, based on: (1) the persistence of [REDACTED]; (2) potential intermediate fate products; and, (3) the possibility or likelihood that this substance may be used as a major substitute for some uses of PFOA, EPA believes more information is needed on the toxicity of [REDACTED] and possibly other environmental degradants, and the fate and physical/chemical properties of [REDACTED]-derived or related polymers in the environment.[143]

The agency added, "EPA expects the PMN substances or the degradants to be highly persistent"[144] and that "there is high concern for possible environmental effects from the potential persistent degradation product [REDACTED]."[145]

To address these concerns, EPA recommended multiple additional tests: reproductive and long-term toxicological testing in rats, a chronic toxicity/carcinogenicity test in rats, and an avian reproduction test in mallard ducks. However, these tests were not required.[146] PSR has asked EPA for the results of any of these health tests, if indeed they were completed, as well as health testing data submitted with the importer's premanufacture notice that was not included in the release of public records. While we received health testing data for unidentified substances that may be for chemical P-11-0091 (the chemical identity was redacted), we did not receive any documents showing completion of the tests for reproductive and long-term toxicological testing, chronic toxicity/carcinogenicity, or avian reproduction. The health testing data PSR received did not appear to show alarming results but also did not appear to test for degradation products of the chemicals – despite the fact that the degradation products of chemical P-11-0091 were the focus of EPA's concern.

Another potential – and unstated – reason for EPA's approval of the chemicals is that EPA generally assumes in its new-chemical reviews that oil and gas chemicals never

EPA OK'D [CONTINUED]

leak, spill, migrate underground, or are otherwise released into the environment accidentally. This assumption is not explicitly stated. Rather, it is apparent in a set of documents that EPA has used for decades to predict exposures to chemicals used in oil and gas drilling and hydraulic fracturing. As analyzed by Partnership for Policy Integrity in a 2016 report, the documents reveal that the agency assumes that any releases of chemicals into the environment will be intentional and controlled, such as disposal of chemical-tainted wastewater into injection wells that EPA assumes will never leak, and the use of wastewater for agriculture.[147] The only exception we are aware of to the agency's assumption that all releases of chemicals will be intentional and controlled was in a 1994 document which said that "several of the surfactants such as alcohol ethoxylates and alkyl phenol ethoxylates, as well as organic in situ crosslinkers such as formaldehyde, are sufficiently volatile to result in air emissions from their use." The same document says, however, that "releases to water are assumed to be negligible."[148] It is a dubious assumption.

EPA's longstanding assumption that accidental releases of chemicals are essentially nonexistent is contradicted by data from EPA itself. As early as 1987, the agency documented unintended releases of drilling mud, fracking fluid, and wastewater in a report to Congress on oil and natural gas wastes.[149] The EPA highlighted spills associated with fracking in its 2016 report on fracking and drinking water.[150] Also in 2016, in a tacit admission that its assumption was unrealistic, EPA told Partnership for Policy Integrity that it had planned to develop a new exposure scenario that accounted for leaks and spills of fracking chemicals.[151] In addition, other public sources show that leaks and spills are common in oil and gas operations. For example, Cabot Oil and Gas Corp., Range Resources Corp., and Noble Energy Inc., have told investors that blowouts, leaks, and/or spills are common risks in oil and gas operations.[152] PSR is not aware that EPA has adopted an updated set of assumptions, but in any event, in 2011, EPA generally did not consider accidental releases of oil and gas chemicals as a pathway of exposure. Making this assumption could have enabled EPA to conclude that human exposure to the chemicals would be limited and thus that there would be minimal harm even from an extremely toxic chemical. This perspective could have influenced the agency's decision to approve the three chemicals. PSR has asked EPA why it approved the chemicals and if the agency's unrealistic exposure assumptions played a role, but as of end-June 2021, has not received a response.

LOCATING WHERE PFAS CHEMICALS HAVE BEEN USED: AN ONGOING CHALLENGE

As previously stated, PSR was able to locate oil and gas wells where PFAS or potential PFAS were used, at least some of which might be chemical P-11-0091. But confidentiality claims and other hurdles make it extremely difficult for the public to know for certain where this particular chemical or other oil and gas chemicals associated with PFAS have or are being used. As is discussed above, people can search for wells in which fracking chemicals were used through the nongovernmental organization FracFocus.[153] In addition, California operates its own searchable database for fracking chemicals.[154] The most accurate way to search for chemicals through these databases is by CAS number.[155] Other ways to search are by specific chemical name or trade name, but these are less accurate because a single chemical can have multiple names or trade names, and people conducting a search might be looking under the wrong name. Yet in many cases, as is the case with chemical P-11-0091, all these searches are impossible because the chemical's CAS number, specific chemical name, and trade name are redacted as trade secrets.

Exemptions under state rules provide several additional ways for oil and gas companies or chemical makers to shield from public scrutiny the use of oil and gas chemicals. For example, state rules typically allow well operators to withhold chemical identities from the public as trade secrets, just as chemical manufacturers or importers are allowed to do under federal law. So even if a chemical importer decided to remove CBI protection from the chemical's identity under federal law, a well operator could still assert that the identity was a trade secret under state rules.[156] State rules also typically do not require chemical manufacturers or importers to disclose their chemicals at all.[157] There is some evidence that manufacturers and importers may not provide all their fracking chemical identities to well operators or owners, who bear the burden of public disclosure under state rules.[158] In any case, if chemical manufacturers do not disclose fracking chemicals to well operators or owners, these actors cannot disclose the chemicals to the public.[159] Finally, most state rules do not require public disclosure of chemicals used in the drilling process that precedes fracking. Therefore, if the chemical P-11-0091 were used for drilling as opposed to fracking, there would be no obligation to disclose the chemical publicly under most state rules. Ohio may be the only exception, although Ohio allows well operators to withhold the identities of drilling chemicals as trade secrets.[160]

It may be possible to locate where PFAS chemicals have been used by relying on provisions added to TSCA by Congress in 2016. But even under those provisions, there remain challenges. Some of the added provisions in TSCA enable state and tribal governments, health professionals and first responders to obtain confidential information about chemicals. The provisions also allow disclosure in situations "pursuant to discovery, subpoena, other court order, or any other judicial process otherwise allowed under applicable Federal or State law."[161] In many of these cases, entities would have to keep the information to themselves and could use it only for limited purposes such as medical treatment,[162] but there is no explicit prohibition on making the information public as part of judicial processes and in other situations.

However, even if officials were to obtain a PFAS chemical's specific identity, especially its CAS number, there is no guarantee that they could require chemical manufacturers or importers to disclose where the chemical had been used. And even if they could, disclosure after an accident has occurred makes it unlikely that first responders will obtain the information in time to provide appropriate treatment to persons who have been exposed to a dangerous substance. Furthermore, as Youngstown, Ohio Fire Department Battalion Chief Caggiano told Partnership for Policy Integrity in 2019, post-incident disclosure deprives first responders of the ability to plan for a hazardous materials response or prevent serious spread of a dangerous pollutant.[163] In addition, there is no guarantee that a chemical's CAS number – if obtained through TSCA – would appear in fracking chemical disclosure records, even if the chemical had been used in oil and gas wells. Exemptions previously discussed would enable oil and gas well operators to withhold such information from these state-level disclosures.

Finally, compliance with terms of the updated TSCA

might be an issue. Reporter Eliza Griswold wrote in her 2019 Pulitzer Prize-winning book, Amity and Prosperity, about residents of western Pennsylvania who had sued well owner Range Resources after suffering health impacts and the deaths of animals that they believed were caused by Range's drilling operations near their homes. The residents requested from Range, among other pieces of information, the full list of chemicals used nearby. Range failed to provide the plaintiffs with a full list despite a court order that was in effect for several years. Range's lack of compliance was likely due in part to the fact that Range did not know some of the trade secret chemicals used by its subcontractors. A judge declined to sanction Range for failing to comply with the order. The inability to obtain the chemical identities made it more difficult for the residents to establish that Range had harmed them and may have influenced two residents to sign a confidential legal settlement that, Griswold wrote, "left both of them feeling angry and defeated."[164] As is suggested by this example, it is possible that oil and gas companies may be unable to comply with some of the provisions of TSCA requiring disclosure of confidential chemical identities. EPA, state government officials, and courts may have to force other companies in the supply chain, particularly chemical manufacturers, to provide this information

RECOMMENDATIONS

Considering the evidence that PFAS substances and/or PFAS precursors are being used in oil and gas wells; given EPA's concerns that a chemical the agency approved for commercial use could degrade into PFOA-like substances that would be toxic, persist in the environment, and bioaccumulate in people's bodies; and in light of the potential that people might be unknowingly exposed to these highly toxic substances, PSR recommends the following:

- **Health assessment.** EPA and/or states should evaluate through quantitative analysis whether PFAS and/or PFAS breakdown products associated with oil and gas operations have the capacity to harm human health. All potential pathways of exposure should be examined, including inhalation, ingestion, and dermal contact.

- **Testing and tracking.** EPA and/or states should determine where PFAS and chemicals that may be PFAS have been used in oil and gas operations and where related wastes have been deposited. They should test nearby water, soil, flora, and fauna for PFAS.

- **Funding and cleanup.** Oil and gas and chemical firms should be required to provide adequate funding for environmental testing and evaluation, and should PFAS be found, for cleanup. If water cleanup is impossible, the companies responsible for the use of PFAS should pay for alternative sources of drinking water.

- **Public disclosure.** Echoing recommendations by Pennsylvania's Attorney General in 2020, governments should require full public disclosure of drilling and fracking chemicals before each oil or gas well can be developed. EPA and/or states should inform communities potentially exposed to PFAS about PFAS contamination risks so that the communities can take actions such as water testing and treatment.

- **Moratorium on PFAS use for oil and gas extraction.** Until testing and investigation are complete, EPA and states should not allow PFAS or chemicals that could break down into PFAS to be manufactured, imported, or used for oil and gas drilling or fracking.

- **Limits on drilling and fracking.** The use of PFAS and of chemicals that break down into PFAS in drilling and fracking should prompt governments to prohibit drilling, fracking, and disposal of related wastewater and solid wastes in areas that are relatively unimpacted by oil and gas pollution, and to increase protections in already-impacted regions. When doubt exists as to the existence or danger of contamination, the rule of thumb should be, "First, do no harm."

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[158] Eliza Griswold. Amity and Prosperity. Farrar, Straus and Giroux (2018), at 259-261 (reporting that well operator Range Resources likely did not know some of the chemicals that its subcontractors were using and that some of the chemical identities were known by a chemical manufacturer, ProTechnics, that refused to reveal some of them). Permittee Range Resources – Appalachia, LLC's Amended Responses and Objections to Appellant's Request for Production of Documents and Request for Admission. Filed with Commonwealth of Pennsylvania Environmental Hearing Board (April 24, 2013) (Range Resources, a well operator, stated in this document that "Some [chemical] manufacturers include very little information about the actual components of a particular product [in Material Safety Data Sheets provided to users of their chemicals]. As a result, Range is currently in the process of seeking additional information from manufacturers that have failed to provide enough information about their products in the MSDS." Range provided specific examples.) (on file with PSR). U.S. House of Representatives Committee on Energy and Commerce, Minority Staff. Chemicals Used in Hydraulic Fracturing (April 2011), at 2, 12 (finding that "in many instances, the oil and gas service companies [that conduct hydraulic fracturing] were unable to provide the Committee with a complete chemical makeup of the hydraulic fracturing fluids they used. Between 2005 and 2009, the companies used 94 million gallons of 279 products that contained at least one chemical or component that the manufacturers deemed proprietary or a trade secret. Committee staff requested that these companies disclose this proprietary information. Although some companies did provide information about these proprietary fluids, in most cases the companies stated that they did not have access to proprietary information about products they purchased 'off the shelf' from chemical suppliers. In these cases, the companies are injecting fluids containing chemicals that they themselves cannot identify.") (on file with PSR).

[159] See, e.g., Petitioners' pleading filed in Robinson Twp. v. Commonwealth, Docket No. 284 MD 2012 (June 9, 2014), at 11 FN6. United State House of Representative Committee and Energy and Commerce, Minority Staff. Chemicals Used in Hydraulic Fracturing (April 2011) (on file with PSR).

[160] Dusty Horwitt. Hydraulic Fracturing Chemical Disclosure: Can the Public Know What's Going Into Oil and Natural Gas Wells? Chapter in Environmental Issues Concerning Hydraulic Fracturing, Kevin A. Schug and Zacariah Hildenbrand, Eds. (Elsevier 2017), at 91, 95.

[161] 15 USC 2613 (d).

[162] 15 USC 2613 (d) (4-7).

[163] Telephone interview with Silverio Caggiano (July 12, 2019).

[164] Eliza Griswold. Amity and Prosperity (2018), at 259-263, 302-304.

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Comment on "Fracking with Forever Chemicals" by Physicians for Social Responsibility, issued July 2021

By: John A. Connor, PE, PG, BCEE, Ileana A.L. Rhodes, PhD, Curtis C. Stanley, PG, CPGS, Elaine Gie, Graham K. Ansell, PhD, Janet K. Anderson, PhD, DABT, Anthony D. Daus, PG, and Dave T. Adamson, PhD, PE, with GSI Environmental Inc., September 2021

The recent publication by attorney Mr. Dusty Horwitt on behalf of the Physicians for Social Responsibility (PSR, see fracking-with-forever-chemicals.pdf (psr.org)) asserts that the U.S. Environmental Protection Agency (USEPA) authorized the unsafe use of per- and polyfluoroalkyl substances (PFAS) for hydraulic fracturing and that these chemicals are widely used by oil and gas operators in a dangerous manner. We find that this article presents an inaccurate and exaggerated picture of the use of PFAS in hydraulic fracturing and the risks posed to public health and the environment.

The facts show that PFAS have been rarely used in oil and gas operations and the limited use that has occurred was principally prior to 2017 and almost exclusively limited to three states, where hydraulic fracturing occurs at great depth and does not pose risk to groundwater resources. None of the alleged health impacts from PFAS that are discussed by PSR are associated with upstream oil and gas activities, nor would such impacts be expected, given the regulatory specifications in place to properly contain drilling and fracturing fluids and protect water resources. Furthermore, PSR misrepresents USEPA's actions in this matter. USEPA did not approve the unsafe use of the three products in question but, in fact, issued an Order to the manufacturer limiting the use of these products with the goal of protecting health and the environment. Furthermore, the applicant did not propose these products for use in hydraulic fracturing nor were they ever used as such.

Further discussion of key points in this regard are summarized below.

1. PFAS fluids have been used in less than 1% of hydraulic fracturing projects nationwide.

PSR obtained information from FracFocus (https://fracfocus.org/), a publicly accessible, national registry, where US oil and gas operators post information on the materials used in their hydraulic fracturing projects. The FracFocus database is managed by the Ground Water Protection Council and the Interstate Oil and Gas Compact Commission – two organizations comprised of state government officials, with the mission of resource conservation and environmental protection. Twenty-five states require or recommend that oil and gas operators disclose their data via FracFocus. Current FracFocus records indicate that the PFAS that have been used in hydraulic fracturing fall into 4 groups: i) perfluoroalkyl alkanes/cycloalkanes, ii) fluoroalkyl alcohol substituted polyethylene glycol, iii) nonionic fluorosurfactants, and iv) polytetrafluoro-ethylene (PTFE). PTFE, which is not mentioned by PSR, is a solid polymer that does not pose any potential for migration within the subsurface. Consequently, we have addressed the use of the prior three categories of PFAS in our evaluation. PSR identifies a fifth chemical group, perfluorinated benzoic acids, but these are not PFAS, consistent with the guidance of the Interstate Technology Regulatory Council (ITRC, 2020).

Of the nearly 184,000 records on hydraulic fracturing projects in FracFocus, only approximately 1600 report the use of PFAS in hydraulic fracturing fluids, which represents less than 0.9% of the hydraulic fracturing projects on record. In other words, over 99% of hydraulic fracturing projects on record have used no such additives. Moreover, contrary to PSR's assertion, applicable regulations mandate protective measures through every step of the well drilling and hydraulic fracturing process to prevent drilling and fracturing fluids from entering groundwater. These measures are discussed further below.

2. Over 99% of the projects on record that used PFAS were located in Texas, Oklahoma, and New Mexico, where hydraulic fracturing

occurs at great depth, nearly all produced water is captured for reinjection into deep brine strata, and impacts by hydraulic fracturing on drinking water aquifers have not been observed and are very unlikely to occur.

Nearly all of records where PFAS are reported to have been used for hydraulic fracturing are in the states of Texas, Oklahoma, and New Mexico. According to the Groundwater Protection Council, the produced water associated with hydraulic fracturing and oil and gas production in these three states is nearly entirely re-injected into deep brine formations located far below the depth of any drinking water aquifers - either to enhance production levels or for permanent disposal (Veil, 2015). These brine fluids have been contained in these deep strata for millions of years and, contrary to statements by PSR, there is no reasonable potential for these natural brines or the produced water added to these brines to move upward to contaminate drinking water, particularly from injection wells designed, constructed, and operated to conform to regulatory requirements for protection of drinking water resources.

Furthermore, given the nature and depth of oil and gas wells, impacts from hydraulic fracturing are very unlikely. According to the FracFocus database, in the states where PFAS fluids were used as additives for hydraulic fracturing, the median depths of the fracturing zones are 5300 feet (Texas), 6900 feet (Oklahoma), and 9500 feet (New Mexico). The hydraulic fractures created in the rock at these depths are far too short to extend upward into drinking water aquifers, commonly found above a depth of 1000 feet. Nor, as suggested by PSR, given the nature of oil and gas operations and the physical-chemical properties of PFAS, could PFAS be released "when gas is burned off from flaring" or "evaporate or disperse as a gas inside the home."

3. The FracFocus records show that the limited use of PFAS occurred principally prior to 2017 and current use is nearly non-existent.

Of all the cases where PFAS has been used as a liquid additive for fracturing fluids, 94% were in the period of 2012 to 2016. In the past two years (2020 – 2021), there are only 9 wells on record where PFAS additives were used (all in Texas and Oklahoma), corresponding to less than 0.6% of the cases where PFAS was used and less than 0.1% of all the hydraulic fracturing projects completed in this time period.

4. None of the PFAS health effects described by PSR have been associated with PFAS use for hydraulic fracturing.

PSR discusses epidemiological studies of PFAS exposure in West Virginia, as well as USEPA concerns about health and ecological effects, and groundwater contamination in Michigan; however, none of these problems are associated with the use of PFAS in hydraulic fracturing. The health effects and public health concerns described by PSR are specific only to the long-chain fully fluorinated alkyl acids, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) and have not been associated with the PFAS used at a small number of hydraulic fracturing sites, specifically, perfluoroalkyl alkanes/cycloalkanes, fluoroalkyl alcohol substituted polyethylene glycols, or nonionic fluorosurfactants. It is incorrect to assume that the health effects often linked to PFOA and PFOS would apply to the PFAS that were used in drilling or fracturing fluids.

5. USEPA did not approve the unsafe use of PFAS in hydraulic fracturing fluids.

PSR's claim that USEPA approved the use of PFAS for hydraulic fracturing, even though USEPA knew this use to be unsafe, is based on their review of three Premanufacture Notices (PMNs) in which a company notified USEPA that certain chemical products containing PFAS might be imported at a future date. However, contrary to PSR's assertion, these submittals neither indicate the products to be unsafe under their proposed use nor constitute an inappropriate approval by USEPA.

Subject to the Toxic Substances Control Act (TSCA), parties who plan to manufacture or import a new chemical substance must submit a PMN, describing the proposed use of the product, its chemical composition, and the potential effects of these chemicals on human health and the environment (40 CFR Part 720). The USEPA reviews the PMN for

completeness and, before adding the information to its national registry of over 86,000 chemical products, can restrict the manufacture and use of the product if deemed necessary to prevent unreasonable risks to health or the environment.

This is exactly what occurred in this case under a Consent Order issued by USEPA to the applicant in October 2011 (USEPA, 2011, Consent Order and Determinations Supporting Consent Order for Premanufacture Notice Numbers P110091, 92, and 93), which considered the potential risks of these products, required testing of its chemical composition and potential health and ecological effects, placed limits on the quantity that could be manufactured or imported and how it could be used, and required that records be maintained regarding manufacturing and distribution. However, it is important to note that the PMNs did not propose to USEPA that these three products would be used for hydraulic fracturing nor is there any record in FracFocus of them having been used in this manner. Quite simply, contrary to the assertions by PSR, USEPA did not approve the unsafe use of these three chemicals for any purpose and, more specifically, was not even asked to approve these chemicals for hydraulic fracturing.

PSR furthermore fails to note that two of the three PFAS products in question were never manufactured or imported. With regard to the third, the PSR paper confirms that there "is no record in FracFocus of this product having been used in ***any*** hydraulic fracking operations in the United States" [emphasis added].

The PSR paper also claims that, even when the USEPA-mandated risk assessments are conducted, the possible impacts associated with products spills, etc., are not addressed. This is simply incorrect, as demonstrated by USEPA guidelines and our own experience. PSR also repeats outdated criticisms of the USEPA TSCA program by the Government Accounting Office (GAO) from 2009 but ignores the significant improvements to the program since that time, which were acknowledged by GAO in 2019. These changes include new restrictions on withholding Confidential Business Information (TSCA Section 14(c)(2)), which were also not considered by PSR. In addition, PSR neglects to consider the other state and federal statutes that require all industrial operations, including hydraulic fracturing, to be protective of water resources and to assess and mitigate risks posed by spills or releases of hazardous chemicals. These laws include the Safe Drinking Water Act, the Clean Water Act, the Resource Conservation and Recovery Act, the Oil Pollution Act, and the Superfund Amendments and Reauthorization Act.

6. Oil and gas drilling and well completion operations incorporate numerous measures to protect groundwater, subject to strict regulations.

PSR appears to misunderstand the nature of oil and gas drilling and hydraulic fracturing operations and the measures that are in place to protect groundwater. Referring to the drilling process, their paper states*, "Chemicals can be injected in this stage of the process to help keep the drill bit cool and to lift rock cuttings out of the well, and at this point in the process, no protective structures are in place to keep those chemicals from entering groundwater."* This is incorrect.

State laws and regulations require protection of water resources during drilling operations (Ground Water Protection Council, 2017). In all oil and gas wells, groundwater is protected by one or more cemented steel casings that extend continuously through the full depth of usable quality groundwater. Under Texas oil and gas rules, for example, "usable quality groundwater" is considered to be water containing less than 3,000 mg/L of dissolved solids – a concentration that incorporates a 3-fold safety factor above the fresh drinking water standard. The protective surface casings are commonly drilled using water-based drillings muds or air rotary drilling to prevent release of hazardous chemicals to groundwater. Below this depth, the well is typically completed with additional sections of casing and cement seals to stabilize the well and further isolate the oil and gas production zone from the overlying usable groundwater. Only once drilling is completed and the vertical and horizontal segments of the well have been properly sealed and pressure tested, are fracturing fluids injected into the well as part of the well completion process.

7. Hydraulic fracturing has not caused widespread groundwater impacts.

With many thousands of hydraulic fracturing projects completed in the US, there is no evidence of "already impacted regions," where hydraulic fracturing has impaired groundwater or surface water, as stated by

PSR. The PSR paper cites a USEPA study listing chemicals used in hydraulic fracturing (USEPA, 2016), but neglects to point out that this study did not report unsafe exposures to these chemicals and that this chemical list includes a number of materials known to be innocuous, such as guar gum, cellulose, and gelatin. PSR also describes cases where health effects were allegedly observed in proximity to hydraulic fracturing operations but fails to note that peer-reviewed scientific studies have repeatedly found these claims to be factually incorrect (e.g., WDEQ, 2019; TAMEST, 2017; McHugh et al., 2016; Connor et al., 2016; McHugh et al., 2015; McHugh et al., 2014; Vidic et al., 2013; API, 2013a, 2013b; Groat and Grimshaw, 2012). Similarly, the USEPA study on hydraulic fracturing "did not find evidence" of "widespread, systemic impacts on drinking water resources in the United States" (USEPA, 2015). With regard to PFAS, recent nationwide testing has found these chemicals to be present in some drinking water systems (USEPA, 2021); however, none of these cases has been found to be related to hydraulic fracturing operations. Nor would such impacts be expected to occur. As noted above, hydraulic fracturing commonly occurs at depths where fractures cannot extend up to groundwater aquifers located thousands of feet above. In addition, wells are constructed to prevent contamination of groundwater, and surface operations are designed to prevent spills to soil and groundwater, including use of secondary containment. However, if and when spills do occur at individual well sites, the operating companies are responsible for assessing and remediating any associated impacts per federal, state, and local regulations.

8. PSR's recommendations regarding hydraulic fracturing are duplicative of existing programs and are not based on objective science.

PSR concludes their paper with six recommendations regarding hydraulic fracturing and the use of PFAS. Our evaluation finds these recommendations to be duplicative of existing programs, unnecessary, and not based on fact. The recommended *health assessment* of PFAS is presently underway at USEPA and numerous other public and private research institutions nationwide. FracFocus provides the recommended *public disclosure* of fracturing chemicals and *tracks the use of PFAS* in these operations – which is why PSR was able to freely access this information. Under existing state and federal regulations, the oil and gas industry is presently required to provide the recommended *funding and cleanup* of environmental impacts associated with its operations. The recommended *moratorium on PFAS use for oil and gas extraction* is unnecessary, as PFAS additives were used in less than 1% of hydraulic fracturing projects, principally over 5 years ago, with current usage being almost nonexistent. Furthermore, as noted above, significant measures are in place to protect groundwater and the environment. Finally, we find that the recommendation that there be *limits on drilling and fracking* is not based on an objective analysis of the facts. There are no "impacted regions" in the US, where hydraulic fracturing has damaged water resources and there is no valid evidence that this technology has impaired public health. The facts show that PFAS use in hydraulic fracturing was limited to a small number of past cases and is very unlikely to pose a risk to public health or the environment.

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Instructions for Reporting PFAS Under TSCA Section 8(a)(7)

U.S. Environmental Protection Agency Office of Pollution Prevention and Toxics
May 2024
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DOCUMENT HISTORY

Document Date	Action
October 2023	Creation of original document and posting to docket and TSCA website
April 2024	Clarifying revisions to Section 2.1.2: Is Your Chemical a PFAS? Removal of references to online reporting guide Edits to Section Byproduct Reporting section to clarify CBI substantiation questions Revisions to Appendix C: Examples of PFAS covered by this rule

HIGHLIGHTS OF REPORTING AND RECORDKEEPING REQUIREMENTS FOR PFAS UNDER TSCA 8(a)(7)

- Reporting is required for any manufacturer (including importer) of a per- or poly-fluoroalkyl substance (PFAS).
- Reporting is required for all PFAS, as defined in 40 CFR 705, that are chemical substances as defined by TSCA, that have been manufactured (including imported) for commercial purposes during this rule's lookback period.
- Information on the reportable chemical substance must be reported during the data submission period (40 CFR 705).
- All reporting sites must report PFAS data electronically, using the section 8(a)(7) web-based reporting tool within EPA's Central Data Exchange (CDX) system. Prior to submitting data, submitters must register with CDX. Ensure that your pop-up blocker is disabled before you begin to use the PFAS section 8(a)(7) tool to complete your form.
- Streamlined reporting is available for importers of articles and for manufacturers of less than 10 kg of a substance used solely for research and development.
- No small manufacturer exemptions are in effect for this data call. You may be required to report under this PFAS data call even if you are not required to report to under other TSCA requirements such as CDR due to a small manufacturer exemption.
- Information submitted under this data call may be claimed as confidential; however, such claims must be made at the time of submission and substantiated in accordance with TSCA and the PFAS data reporting rule. Submitters must provide upfront substantiation of all confidentiality claims except for claims made for import or yearly production volume information. Submitters who do not know the underlying identity of the chemical other than a generic chemical name (i.e., do not know a CASRN, or TSCA Accession or LVE numbers) are not required to assert and substantiate a CBI claim for chemical identity. Reporters using the article importer form also are not required to assert and substantiate a CBI claim for specific chemical identity. Certain processing and use data elements or a response that is designated as "not known or reasonably ascertainable" may not be claimed as confidential (40 CFR 705.30).
- Visit the section 8(a)(7) rule website (*https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-section-8a7-reporting-and-recordkeeping*) for other guidance materials and contact information for technical assistance.

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PREFACE

The primary goal of this document is to help the regulated community comply with the requirements of the TSCA Section 8(a)(7) Reporting and Recordkeeping Requirements for Perfluoroalkyl and Polyfluoroalkyl Substances rule, hereafter referred to as section 8(a)(7) reporting. This document does not substitute for that rule, nor is it a rule itself. It does not impose legally binding requirements on the regulated community or on the U.S. Environmental Protection Agency (EPA).

Manufacturers (including importers) are required by the section 8(a)(7) rule to report to EPA information concerning the manufacturing, use, disposal, and environmental and health effects of certain Perfluoroalkyl or Polyfluoroalkyl Substances (PFAS). Manufacturers (including importers) are subject to the reporting requirements based on manufacturing (including importing) activities conducted since January 1, 2011. This is a one-time reporting event to provide greater transparency on the uses and risks associated with PFAS and is mandated by the Fiscal Year 2020 National Defense Authorization Act (NDAA).

Data submissions are due by the close of the submission period. The submission period will begin twelve months following the effective date of the final rule and will last for six months. PFAS manufacturers will have 18 months from the effective date of the rule to report: May 8, 2025. For small manufacturers (using the same definition as 40 CFR 704.3) whose PFAS reporting obligations are exclusively due to article import, the submission period will last twelve months, such that all reporting from these small article importers is due two years from the effective date of the final rule: November 10, 2025. Data must be submitted using the "TSCA section 8(a)(7) PFAS data call rule" service via EPA's Central Data Exchange (CDX), hereafter referred to as the "reporting tool." Submitters are required to use the reporting tool to prepare their submissions. The reporting tool guides users through a "hands-on" process of creating an electronic submission. A user guide on how to register for CDX and access the reporting tool is available on the *TSCA section 8(a)(7) Reporting and Recordkeeping Requirements for Perfluoroalkyl and Polyfluoroalkyl Substances* website at *https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-section-8a7-reporting-and-recordkeeping*.

This instructions document contains the following chapters and appendices:

- Chapter 1 – Introduction to the TSCA section 8(a)(7) PFAS reporting rule.
- Chapter 2 – Reporting requirements to determine which chemical substances are reportable, who must report, and what information must be reported.
- Chapter 3 – When you must report.
- Chapter 4 – Instructions for completing section 8(a)(7) reporting.
- Chapter 5 – How to obtain copies of documents cited in this Instructions document.
- Appendix A – Glossary.
- Appendix B – Key Comparisons between Section 8(a)(7) Data Call and CDR

- Appendix C – Examples of PFAS covered by this rule.
- Appendix D – Descriptions of codes for reporting *Processing or Use Operations, Industrial Sectors, Industrial Function Categories,* and *Consumer and Commercial Product and Function Categories*.

1. Introduction

1.1 Background and Statutory Authority

In accordance with obligations under TSCA section 8(a)(7), as amended by the National Defense Authorization Act for Fiscal Year 2020, EPA is requiring persons that manufacture (including import) or have manufactured these chemical substances for commercial purposes in any year since January 1, 2011, to submit information to EPA regarding PFAS uses, production volumes, byproducts, disposal, exposures, and existing information on environmental or health effects.

This document provides detailed information and examples to assist manufacturers (including importers) in reporting under TSCA section 8(a)(7). Appendix A of this document provides a glossary of terms, which may help you to understand the reporting requirements.

This document is not a substitute for the TSCA section 8(a)(7) PFAS rule in 40 CFR Part 705. To the extent that any inconsistencies exist between the section 8(a)(7) rule and this document, the requirements as promulgated in the rule should be followed. You should carefully review 40 CFR Part 705 and the final rule preamble (available in this rule's docket at *www.regulations.gov*; docket ID EPA-HQ-OPPT-2020-0549) to determine whether you are required to report information under the section 8(a)(7) rule.

1.2 Duplicative reporting

Your site may have already reported some section 8(a)(7) data to EPA through another EPA program. If that is the case, the site should determine whether EPA has identified such reporting as "duplicative" in the section 8(a)(7) rule. If EPA has identified the reporting as duplicative, your site is not required to re-report duplicative information, but must submit a report and include all information required by this data call that has not been previously reported to EPA. Information that has been reported for some but not all years from 2011 to 2022 must be reported for the "missing" years. Information that has been previously reported, but not to the level of detail required by this data call, or using exemptions not applicable to this data call, must be reported under this data call to the level of detail required, if known to or reasonably ascertainable by you. In the event that new, more accurate, or more detailed information has become known to or reasonably ascertainable by the site, that information must be reported under this data call.

The electronic reporting system will allow you to indicate that certain information has already been reported to EPA. EPA has identified data elements that could have been previously reported under Chemical Data Reporting (CDR); Toxics Release Inventory (TRI) reporting, also known as section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA 313); Greenhouse Gas Reporting (GHGRP); and TSCA sections 8(d) and 8(e). Additionally, there may be limited overlap between forms submitted under section 8(a)(7) reporting in the event

that a reportable PFAS is produced as a byproduct during manufacture, processing, or disposal of another reportable PFAS.

The section 8(a)(7) reporting software will identify the data elements that could contain information already reported to EPA. For these data elements, you may indicate if your company has already reported the information to EPA. You must clearly indicate where the information can be found (i.e., which reporting program) and when that information was submitted (i.e., which year). **Information must have been reported *as required by the section 8(a)(7) rule***; for example, other programs may have exemptions, such as for articles or impurities, that could mean information reported to those programs was not reported as required by this data call.

EPA anticipates that the primary program with "duplicative reporting" is Chemical Data Reporting (CDR). Two other EPA programs that have minor overlap with section 8(a)(7) include the Toxics Release Inventory (TRI) and the Greenhouse Gas Reporting Program (GHGRP).

Note, however, that these programs both cover only a limited subset of the PFAS covered by section 8(a)(7) and have thresholds for reporting that do not apply to this data call. Therefore, you may be required to report under this data call even if you were not required to report under TRI or GHGRP. Further, due to differences in how data are to be reported to those programs, reporting to TRI or GHGRP may not fulfill the requirements of this data call. Some health or environmental information may also have been reported under TSCA section 8(d) or TSCA section 8(e) or another authority.

Note that information reported on pre-manufacture notices (PMNs) or low volume exemptions (LVEs) generally does not fulfill requirements under section 8(a)(7), as PMNs and LVEs reflect information before manufacture of a substance commences.

Information reported to entities other than EPA, such as state agencies, or provided to EPA outside a formal EPA reporting program (such as comments provided on a proposed rule), ***does not*** fulfill your requirement to report to EPA under section 8(a)(7) and cannot be cited as duplicative reporting.

EPA expects that even when a company has previously reported some section 8(a)(7) information, that information will constitute only a minority of information to be reported under this data call.

Information that may have previously been reported under CDR includes:

(1) Physical state of the PFAS pursuant to § 711.15(b)(3)(C)(ix);

(2) Industrial processing and use type, sector(s), functional category(ies), and percent of production volume for each use, pursuant to § 711.15(b)(4)(i)(A) through (D);

(3) Consumer and/or commercial indicator, product category(ies), functional category(ies), percent of production volume for each use, indicator for use in

products intended for children, and maximum concentration in the product, pursuant to § 711.15(b)(4)(ii)(A) through (F);

(4) Number of workers reasonably likely to be exposed for each combination of industrial processing or use operation, sector, and function, pursuant to § 711.15(b)(4)(i)(F), and the number of commercial workers reasonably likely to be exposed when the substance is used in a commercial product, pursuant to § 711.15(b)(4)(ii)(G).

Information that may have been reported to TRI includes:[1,2]

(1) Total volume recycled on-site

(2) Description of disposal process(es)

(3) Total volume released to land

(4) Total volume released to water

(5) Total volume released to air

(6) Total volume incinerated on site[3]

Information that may have been reported to GHGRP includes:[1]

(1) Production volume (imported)

(2) Volume directly exported

(3) Total volume incinerated on site

[1] Due to differences in reporting requirements, exemptions, and other programmatic requirements, reporting to TRI and GHGRP may not meet the requirements of TSCA section 8(a)(7). Carefully review any previous TRI or GHGRP submissions and calculation methods to determine if you may claim duplicative reporting. You may claim duplicative reporting for TRI and/or GHGRP only if the data were reported ***as required by the section 8(a)(7) rule*.**

[2] Only certain PFAS chemicals are reportable under TRI. Most PFAS were added to the TRI chemical list for 2020 reporting, while some chemicals meeting the definition of PFAS used for PFAS 8(a)(7) reporting have been reportable since before 2011. Note that the TRI chemical list includes certain chemicals as unspecified isomers, such as dichloropentafluoropropane, which could include both chemicals considered to be PFAS and chemicals not considered to be PFAS. In the event you know which isomer(s) were used at the site, you must report the specific isomers for PFAS 8(a)(7) reporting and may not consider reporting to TRI under a mixed isomer listing as duplicative.

[3] Carefully review any incineration data reported to TRI to determine if it is duplicative. To claim duplicative reporting, EPA must be able to determine the total volume of the chemical incinerated on site. EPA anticipates that many reporters' TRI reports will not fulfill the requirements of Section 8(a)(7) for the total volume incinerated on site.

Information that may have been reported under TSCA section 8(d) or 8(e) or another authority includes:

(1) Environmental and health effects (OECD harmonized template)

(2) Environmental and health effects study report

(3) Environmental and health effects supporting information

Table 1-1Table 1-1 shows some examples of how companies may consider prior reporting.

Table 1-1. Examples of prior reporting impacts on PFAS data call reporting

Previous Reporting	Site section 8(a)(7) responsibilities
A manufacturer previously reported on Example PFAS A under 2020 CDR. That report included information required by section C of this data call, from 2016 through 2019. Most information required by section C was reported for only the principal reporting year, 2019, and some information for section C was reported for 2016-2018. The site started manufacturing the PFAS in 2015 but did not meet the CDR reporting threshold for that year. The manufacturer continued to produce Example PFAS A in the years since its last CDR report.	The manufacturer considers whether any exemptions applied to the prior CDR reporting that are not available under this rule. The manufacturer determines that the data previously submitted to CDR did not exempt any activities or quantities that would be reportable under this rule, and therefore may be considered duplicative. For section C, the manufacturer indicates that data were already reported to CDR for the applicable fields for 2019, completing the fields for "site-limited?" and recycling, which are not reported to CDR. The manufacturer also indicates the data were already reported to CDR for the fields that were reported for 2016-2018. The manufacturer fills in the remaining section C information for 2016-2018 and all section C information for 2015 and 2020-2022. The manufacturer fills in information for 2015-2022 in all other sections of its PFAS data call reports, as that information has not been reported to EPA for any year.
A manufacturer previously reported information about Example PFAS B, which was manufactured from 2012-2015, to the 2016 CDR. At the time of 2016 CDR submission, several required data fields were not known to or reasonably ascertainable by the company (NKRA). However, the company since learned additional information about the chemical.	The manufacturer indicates duplicative reporting for the data that was known to the site and submitted to EPA for 2012-2015. The manufacturer must report newly acquired information to this PFAS data call for fields reported as "NKRA" to CDR for 2012- 2015. The manufacturer may indicate duplicative reporting for remaining fields that were originally reported as "NKRA" and for which the manufacturer has not acquired new information.
Example Company C manufactures Example PFAS C and has begun gathering and compiling information about this chemical for 2024 CDR (for activities from 2020-2023). The company's 2024 CDR report will not be submitted before the end of the section 8(a)(7) submission period.	The company must report the 2020-2022 information under section 8(a)(7) reporting, even if the information will be reported to EPA in the future. EPA encourages submitters to review their in- progress CDR submissions in gathering data for section 8(a)(7) submissions, and vice versa, to reduce overall reporting

Previous Reporting	Site section 8(a)(7) responsibilities
	burden.
Example Company D imported Example PFAS D at one site in 2015. 10,000 pounds of Example PFAS D was imported as a component of an article, and 50,000 pounds was imported in a mixture. The company reported Example PFAS D to CDR for 2015, reporting on the 50,000 pounds imported in the mixture. The company did not consider the 10,000 pounds of Example PFAS D imported as articles, which are exempt for CDR reporting.	The company must newly report all information for Example PFAS D under this data call. Because information reported to CDR excluded quantities imported in articles, which are not exempt under this data call, the information was not previously reported as required by this data call. The site may not indicate duplicative reporting.
Example Company E imported an article containing Example PFAS E in 2012, 2013, and 2017, but has not been previously required to report this information to any EPA programs. The site reported information about this chemical to the state of Washington's Department of Ecology pursuant to the state's requirements for chemicals in children's products.	The company must report to EPA all information required by this data call for 2012, 2013, and 2017, and indicate that Example PFAS E was not produced in the other years. Reporting to a state program does not fulfill or reduce any requirements for reporting under this PFAS data call.
Example Company F manufactured 1,000 pounds of Example PFAS F each year during 2019, 2020, and 2021. Example PFAS F was added to the TRI chemical list for 2020 reporting and was not TRI-reportable for 2019. Each year, 50 pounds of the PFAS were manufactured and used for quality control in a laboratory on-site. All Example PFAS F produced at Example Company D was disposed of in the site's on-site landfill. After determining that the quantity of Example PFAS F used in the laboratory was exempt from TRI reporting, Company C reported 950 pounds of Example PFAS F releases to TRI for 2020 and 2021.	The company must report all information about Example PFAS F for 2019, because no TRI report was filed for that year. The site may not indicate duplicative reporting for release quantities for 2020 and 2021, because the quantities reported to TRI excluded laboratory uses that are not exempt under Section 8(a)(7) reporting. The company instead reports 1,000 pounds of land disposal for 2020 and 2021. The company may indicate duplicative reporting for types of disposal processes and the quantities released to air, water, and recycled on-site.

2. Reporting Requirements

PFAS data reporting rule requirements apply to certain persons that manufacture (including import) or have manufactured PFAS in any year since January 1, 2011. The term "PFAS" is defined in Appendix A and examples of PFAS are provided in Appendix B. Please note that any use of the term "manufacture" in this document will encompass "import" and the term "manufacturer" will encompass "importer."

For reporting to the PFAS data reporting rule, manufacturers (including importers) are required to use the section 8(a)(7) reporting tool via EPA's CDX to submit information in response to the requirements of the section 8(a)(7) rule (40 CFR Part 705). You must register with CDX to submit online, and you must register the name of the company on whose behalf you are submitting. EPA does not accept paper submissions or electronic media (diskette, CD-ROM, etc.) for any section 8(a)(7) submission (40 CFR 705).

Note that many aspects of reporting for this PFAS data reporting rule are similar to Chemical Data Reporting (CDR), but there are important differences. Even if you have reported previously under the CDR or were exempt from reporting under CDR, you should carefully review the reporting requirements for this rule to ensure you report correctly. Key comparisons between section 8(a)(7) and CDR are outlined in Appendix B of this document.

You should consider the following three steps to determine whether you are required to report for each PFAS chemical substance that you domestically manufacture (including import) into the United States **during each year since** 2011 (i.e., consider calendar years 2011 through 2022):

- Step I: Is your chemical substance subject to PFAS 8(a)(7)?
- Step II: Do you qualify for streamlined reporting?
- Step III: What information must you report?

This chapter discusses each of these steps and the associated reporting requirements in more detail.

2.1 Step I: Is Your Chemical Substance Subject to section 8(a)(7)?

For the purposes of the section 8(a)(7) Reporting Rule, *per- and polyfluoroalkyl substances* or *PFAS* means any chemical substance that contains at least one of these three structure units:

1) R-(CF_2)-CF(R')R'', where both the CF_2 and CF moieties are saturated carbons
2) R-CF_2OCF_2-R', where R and R' can either be F, O, or saturated carbons
3) $CF_3C(CF_3)$R'R'', where R' and R" can either be F or saturated carbons.

This definition may not be identical to other definitions of PFAS used within EPA and/or other organizations. See Section 2.1.2 for further description of these structures. To assist potential reporters with determining whether certain substances may be covered under this structural definition, EPA has identified specific PFAS covered by this rule. This non-exhaustive list is available in EPA's CompTox Dashboard (*https://comptox.epa.gov/dashboard/chemical-lists/PFAS8a7*) and a limited version including only chemicals on the public TSCA Inventory or with low-volume exemptions is included as Appendix B in this guidance document.

Note that the manufacture of PFAS as a byproduct, an impurity, or a non-isolated intermediate **is not** exempt for the purpose of this rule, unlike CDR reporting. However, because entities that import of municipal solid wastes (MSW) for the purpose of disposal or destruction cannot know or reasonably ascertain that they imported PFAS in the MSW streams, these waste management activities are not within the scope of this rule's reporting requirements. Per 40 CFR 705.15, "reporting under this part is not required for the import of municipal solid waste streams for the purpose of disposal or destruction of the waste."

2.1.1 Is Your Chemical Substance Manufactured for Commercial Purposes During the Reporting Period?

The first step in determining your reporting requirements is to determine whether you meet the definition of manufacture or manufacturer. The following manufacturing-related terms are defined below:

- ***Manufacture*** – To import into the customs territory of the United States (as defined in general note 2 of the Harmonized Tariff Schedule of the United States), produce, or manufacture for commercial purposes. (40 CFR 705.3)
- ***Manufacture for commercial purposes*** – (1) To import, produce, or manufacture with the purpose of obtaining an immediate or eventual commercial advantage for the manufacturer, and includes among other things, such "manufacture" of any amount of a chemical substance or mixture:

  (i) For commercial distribution, including for test marketing.

  (ii) For use by the manufacturer, including use for product research and development, or as an intermediate.

  (2) Manufacture for commercial purposes also applies to chemical substances that are produced coincidentally during the manufacture, processing, use, or disposal of another chemical substance or mixture, including both byproducts that are separated from that other substance or mixture and impurities that remain in that chemical substance or mixture. Such byproducts and impurities may, or may not, in themselves have commercial value. They are nonetheless produced for the purpose of obtaining a commercial advantage since they are part of the manufacture of a chemical product for a commercial purpose (40 CFR 705.3).

For purposes of section 8(a)(7) reporting, a chemical substance is manufactured (including imported) only if it is domestically produced or imported for commercial purposes. See TSCA section 8(f), TSCA section 3(9), and 40 CFR 704.3, which includes a parallel definition of "Import for commercial purposes." In the case of chemical substances manufactured (including imported) by one person on behalf of another person, the manufacturer is the person actually manufacturing the chemical substance.

As identified above, the term *manufacture for commercial purposes* means that the chemical substance is produced for the purpose of obtaining an immediate or eventual commercial advantage. Manufacture for commercial purposes also applies to chemical substances that are produced coincidentally during the manufacture, processing, use, or disposal of another chemical substance or mixture, including both byproducts that are separated and impurities that remain in a chemical substance or mixture (40 CFR 705.3). Certain activities are not considered "manufacture for a commercial purpose" (e.g., non-commercial R&D activities such as scientific experimentation, research, or analysis conducted by academic, government, or independent not-for-profit research organizations, unless the activity is for eventual commercial purposes) and are not subject to the reporting requirements in this rule.

2.1.1.1 Changes to Company Ownership or Legal Identity

Under 40 CFR 705, the reporting obligation falls to the "person who manufactured (including imported)" a chemical substance that is a PFAS. EPA recognizes that in some cases, business transactions occurring during the reporting period have led to questions about who is now the "person who manufactured." The scenarios in *Fact Sheet: Reporting After Changes to Company Ownership or Legal Identity* are intended to serve as a general aid in appropriately resolving these questions, but they will not necessarily account for all the relevant circumstances of a particular transaction (*note that while this fact sheet was developed for CDR, changes in company ownership or legal identity are to be handled the same for section 8(a)(7) reporting as for CDR)*. It is ultimately the manufacturer's responsibility to report appropriately under this data call, notwithstanding the complexity of its own business transactions.

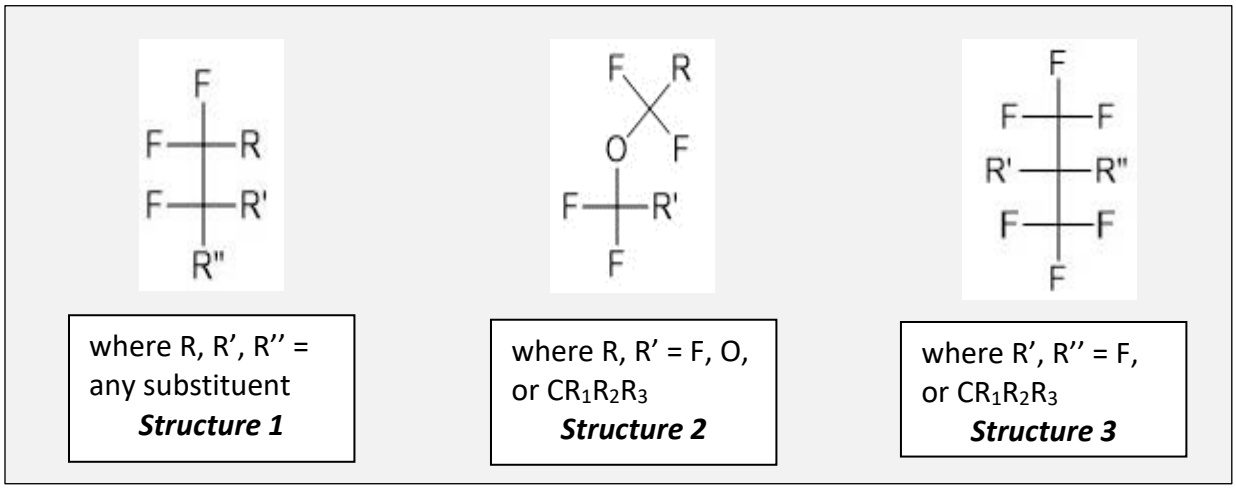
2.1.2 Is Your Chemical Substance a PFAS?

For the purposes of this action, the definition of PFAS includes any chemical substance that structurally contains at least one of the following three sub-structures. Note that in these formulas, R refers to the atom directly adjacent to the backbone:

1) R-(CF_2)-CF(R')R'', where both the CF_2 and CF moieties are saturated carbons (since the R groups are not defined, R, R', and R'' may be any substituent).

2) R-CF_2OCF_2-R', where R and R' can either be F, O, or saturated carbons (i.e., R and R' may be any of the following: a fluorine atom, an alcohol or ether; or any substituent bonded to the backbone by a saturated carbon atom such as a CH_2 group).

3) $CF_3C(CF_3)R'R''$, where R' and R" can either be F or saturated carbons (i.e., R' and R" may be a fluorine atom or any substituent bonded to the backbone by a saturated carbon atom such as a CH_2 group).



This definition may not be identical to other definitions of PFAS used within EPA and/or other organizations. To assist potential reporters with determining whether certain substances may be covered under this structural definition, EPA has identified specific PFAS covered by this rule. This non-exhaustive list is available in EPA's CompTox Dashboard and a limited version including only chemicals on the public TSCA Inventory or with low-volume exemptions as of the publication of this guidance document is included as Appendix B in this guidance document. Note that the CompTox list may change as chemicals are added to the Dashboard.

Manufacturers must consider all manufacturing activities during the reporting period, which begins January 1, 2011. If a manufacturer has manufactured PFAS for commercial purposes in any year since January 1, 2011, they would be required to report under this rule even if they are not currently manufacturing PFAS.

This rule is limited to manufacturers (including importers) of PFAS that are considered a "chemical substance" under TSCA section 3(2). This rule does not require reporting on activities that are excluded from the definition of "chemical substance" in TSCA section 3(2)(B).

Under TSCA section 3(2), "chemical substance" means any organic or inorganic substance of a particular molecular identity, including (1) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and (2) any element or uncombined radical. This rule does not require reporting on activities that are excluded from the definition of "chemical substance" in TSCA section 3(2)(B). The term "chemical substance" does not include: "(i) any mixture, (ii) any pesticide (as defined by the

Federal Insecticide, Fungicide, and Rodenticide Act) when manufactured, processed, or distributed in commerce for use as a pesticide, (iii); tobacco or any tobacco product, (iv) any source material, special nuclear material, or byproduct material (as such terms are defined in the Atomic Energy Act of 1954 and regulations issued under such Act), (v) any article the sale of

which is subject to the tax imposed by Section 4181 of the Internal Revenue Code of 1954 (determined without regard to any exemptions from such tax provided by section 4182 or 4221 or any other provision of such Code) and any component of such an article (limited to shot shells, cartridges, and components of shot shells and cartridges), and (vi) any food, food additive, drug, cosmetic, or device, as defined in section 201 of the Federal Food, Drug, and Cosmetic Act, when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic or device" [15 USC 2602(2)(B)].

Even though the definition of chemical substance excludes mixtures, PFAS as a chemical substance may be present in a mixture. Therefore, this rule requires reporting on each chemical substance that is a PFAS, including as a component of a mixture. This rule does not require reporting on components of a mixture that do not fall under the structural definition of PFAS.

2.2 Step II: Do You Qualify for Streamlined Reporting?

If you determined from Step I that you manufacture (including import) a reportable PFAS for commercial purposes, Figure 2-1Figure 2-1 presents a decision logic diagram that may help you determine whether you are a manufacturer (including importer) who must report with the Standard Form or if you may qualify for streamlined reporting. The following subsections explain each question in greater detail. Note that unlike CDR reporting, no reporting exemptions apply to section 8(a)(7).

2.2.1 Did you import an article containing a reportable PFAS?

If you imported an article containing PFAS, you may use a streamlined Article Import form. This streamlined form does not require all information required for the standard form; when you select "article import reporting" in the section 8(a)(7) reporting tool, the program will show only fields required for this streamlined reporting. Only certain fields in Sections A, B, and C are required for the streamlined article importing. Further, because importers may not know or be able to ascertain how much PFAS is contained within the articles, the article import form allows production volume to reported as the total weight of the imported articles or as the quantity of articles imported (see Section 4.7.2.24.7.2.2), rather than weight of the PFAS. If you have any additional information, such as an SDS or information about disposal, report that information in the Optional Information section of the form (see Section 4.12).

Some sites may both import a PFAS in an article and otherwise manufacture the same PFAS (i.e., domestically manufacture or import other than in an article). In that case, you may choose to either report the imported article and otherwise manufactured PFAS separately, using the streamlined article import form for the imported article and using the standard form for the otherwise manufactured PFAS, or you may include the information for the imported article within the standard form, submitting one standard form for all PFAS produced and imported by the site.

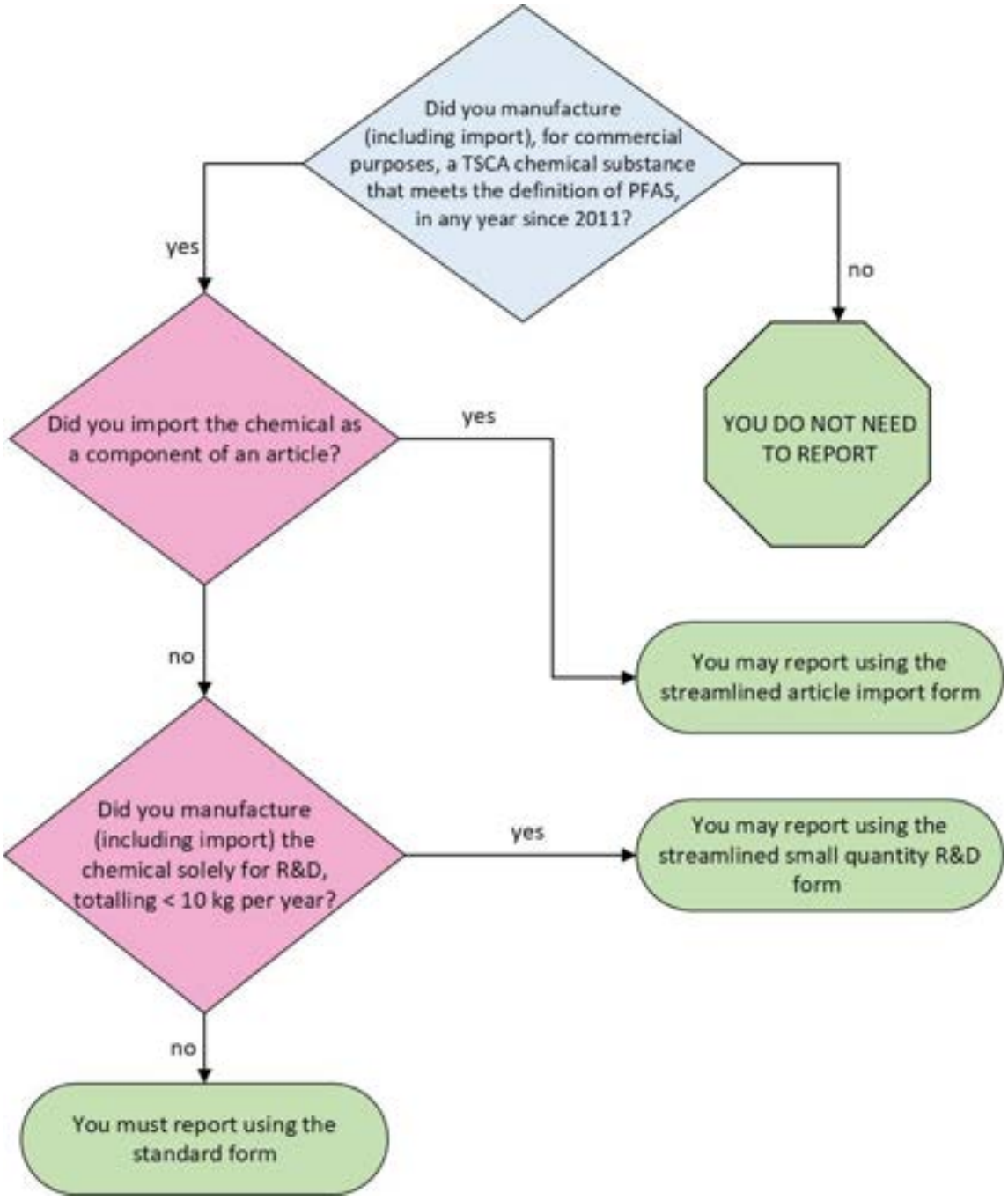


Figure 2-1. Decision Logic Diagram for Evaluating Step II

If you are unsure whether you are importing an article, refer to the CDR "Imported Articles" factsheet at *https://www.epa.gov/chemical-data-reporting/tsca-chemical-data-reporting-fact-sheet-imported-articles-2020*. The TSCA definition of an article is the same for both CDR reporting, as referenced in this factsheet, and for PFAS section 8(a)(7) reporting (40 CFR 705.3). However, recall that while importing an article is exempt from CDR, it is **not** exempt from section 8(a)(7) reporting. If you import an article containing a chemical substance that is a PFAS, you may be eligible to use the streamlined Article Import form, but you **are not** exempt from reporting. You have until May 8, 2025, to report. However, if you meet the following two criteria, you have until November 10, 2025, to report: (1) are considered a small manufacturer pursuant to 40 CFR 704.3 (see Appendix A); and (2) have reporting obligations under this rule exclusively due to importing articles.

2.2.2 Did you manufacture a reportable PFAS in quantities below 10 kg per year exclusively for purposes of research and development (R&D)?

Persons who manufacture (including import) PFAS in small quantities solely for research or analysis for commercial purposes may report using the streamlined small quantity R&D form. The streamlined small quantity R&D form requires reporting only of the chemical substance identification information (see Section 4.3), domestic manufacture and imported volumes, indication of whether the substance was imported but never on site, and an optional additional information field.

Note that any PFAS manufactured for commercial purposes is reportable under this data call. "Manufacture for commercial purposes" encompasses any importing, production, or other manufacturing activities with the purpose of obtaining an immediate or eventual commercial advantage and includes chemicals "for use by the manufacturer, including use for product research and development." R&D substances which meet the scope of "manufactured for commercial purposes" are to be reported under this rule, even if the PFAS itself was not later commercialized. See Section 2.1.12.1.1 for additional guidance on determining if a PFAS was manufactured for commercial purposes."

Some sites may both manufacture a PFAS in small quantities for R&D and otherwise manufacture the same PFAS (i.e., domestically manufacture or import). In that case, your site does not qualify for use of the streamlined form. The streamlined form is limited to persons manufacturing (including importing) PFAS ***solely*** for research or analysis.

Example 2-1. Example Company G produces Example PFAS G at one site. Example PFAS G was produced in amounts of 3 kg in 2011, 7 kg in 2012, and 6 kg in 2013. Example PFAS G was not produced during any other year since 2011 and the quantities produced were used exclusively for research and development.

Because Example PFAS G is used only for research and development, and the volume manufactured was less than 10 kg each year, Example Company G reports using the streamlined R&D form for Example PFAS G.

2.3 Step III: What Information Must You Report?

Once you determine from Steps I and II that you are a manufacturer (including importer) of a reportable PFAS and are required to report, this section will help you determine what information you must report.

If you are required to report and do not qualify for either streamlined form, you are required to report all information described in 40 CFR 705. Importers of PFAS-containing articles and manufacturers (including importers) of small R&D quantities may use streamlined forms, which include only the data elements that EPA believes will be known to or reasonably ascertainable to manufacturers in those situations. The online reporting software will guide you through the data elements required for each form.

Basic company and site identification information, (submitted on Part I of the form) is required by 40 CFR 705.15(a)(1). Chemical identification and information pertaining to the manufacture (including import) of chemical substances (described in *Part II – Section A*) is required by 40 CFR 705.15(a)(2). Note that the basic company and site information is reported once per site, while the manufacturing information is reported separately for each reportable PFAS at the site. Industrial processing and use, and consumer and commercial uses of the chemical substance (described in *Part II – Section B*) is required by 40 CFR 705.15(a)(3).

Information about byproducts (described in *Part II – Section D*) is required by 40 CFR 705.15(a)(3). Information about the environmental and health effects of the PFAS (described in *Part II – Section E*) is required by 40 CFR 705.15(f). Information about worker exposure to the PFAS (described in *Part II – Section F*) is required by 40 CFR 705.15(g). Information about the release or disposal of the PFAS (described in *Part II – Section G)* is required by 40 CFR 705.15(h).

Example 2-2. Example Company H manufactures 8 kg of Example PFAS H in 2017 for on-site R&D operations in development of a new cleaning product. The company scales up R&D for this substance and manufactures 100 kg of Example PFAS H in 2018. The company then discontinues R&D and does not ultimately commercialize Example PFAS H. Example PFAS H is not manufactured after 2018.

Example PFAS H is manufactured for commercial purposes because Example Company H manufactured the chemical with the purpose of obtaining an eventual commercial advantage, so Example Company H must report the substance, even though it was not ultimately commercialized. For 2017, the company manufactured < 10 kg of the substance for R&D and meets the requirements for the R&D form. For 2018, the company manufactured > 10 kg so exceeds the threshold for the R&D form. The company may take one of two actions:

1) Use the R&D form to report for 2017 and the standard form for 2018

2) Report for both 2017 and 2018 on one standard form, completing all fields on the form for both years.

Example 2-3. Example Company I begins importing an article containing Example PFAS I in 2017 and continues importing the article through 2022. Example PFAS I provides stain resistance in a finished textile product. Example Company I does not produce or import any other products containing Example PFAS I.

Because Example PFAS I is only imported in an article, Example Company I reports for this chemical using the streamlined article importer form.

3. When You Must Report

You are required to report information pertaining to each calendar year since January 1, 2011 through December 31, 2022, in which you manufactured a PFAS. The submission period begins twelve months after the effective date of the section 8(a)(7) final rule and lasts for six months. Therefore, reporting is due 18 months after the effective date of this final rule: May 8, 2025. Small manufacturers (per 40 CFR 704.3) whose PFAS reporting obligations are exclusively due to importing articles have an additional six months to report. These small article importers have 24 months from the effective date of the final rule to report: November 10, 2025.

Your report must be submitted to EPA using the electronic section 8(a)(7) reporting tool ("reporting tool") via EPA's Central Data Exchange (CDX) no later than the close of the submission period. You should note that registration with CDX is required prior to accessing the reporting tool to submit your PFAS data call information (40 CFR 705.35). To get you started, guides are available on EPA's website:

- CDX Registration Guide, which covers the specifics of CDX registration (https://cdx.epa.gov/About/UserGuide)

If you are required to report, failure to file your report during this period is a violation of TSCA sections 8(a) and 15 and may subject you to penalties (40 CFR 705.1).

4. Instructions for Completing Section 8(a)(7) Reporting

This chapter will help you complete section 8(a)(7) reporting. Section 4.1 describes how to certify your submission. Section 4.2 discusses the reporting standard – the effort required to comply with the PFAS data call. Sections 4.3 through 4.11.3 provide information to help you complete each required section of the reporting form.

You are required to use the section 8(a)(7) online reporting tool in CDX to complete and submit a reporting form for each reportable PFAS. If you are reporting information for more than one PFAS at your site, you must report information for each reportable PFAS on its own form. If you are reporting for multiple sites, you must submit separate forms for each site. In most cases, you will submit exactly one form per chemical at the site. However, in certain cases if you are an article importer, you may submit multiple forms for the same chemical at one site; see Section 2.22.2.

The standard reporting form is comprised of a certification statement and three parts, as follows:

- The certification statement and Part I of the form are completed once per reporting site. Part I contains company, site, and contact information, some of which is pre-populated based on the information in your CDX account for the site. Once this section has been completed for a reporting site, the reporting tool will automatically populate Part I with this information for any additional forms for the site.
- Part II – Sections A – C are completed for each reportable PFAS at the site and contains information associated with the identity, manufacture, and properties of the chemical substance.
- Part II – Section D is completed for the byproducts produced during manufacture of each PFAS.
- Part II – Section E is completed for each reportable PFAS at the site and contains information associated with the environmental and health effects of the PFAS.
- Part II – Section F is completed for each reportable PFAS at the site and contains information associated with workers' exposure to the PFAS.
- Part II – Section G is completed for each reportable PFAS at the site and contains information associated with the disposal of the PFAS.
- Part II – Section H is an optional free text field that allows submittal of any additional information.
- Part III is completed for each reportable chemical substance at the site for which confidentiality claims are made for one or more data elements, when substantiations of the confidentiality claims are required at the time of data submission.

The streamlined article import and small-quantity R&D forms reduce the number of fields to be reported. Sections D – G are not required on these forms and the requirements for Sections A – C are reduced. If any information in the omitted sections is known to you, you may report that information in the free text field in Section H.

Note: Items such as the validation page and the SRS search page will appear in separate windows. Ensure that your pop- up blocker is disabled before you begin to complete PFAS section 8(a)(7) reporting.

4.1 Certification

Your submission(s) must be certified, indicating that your submitted information has been completed in compliance with the PFAS data call requirements, such as all information known or reasonably ascertainable is submitted, and that the confidentiality claims made in this report are true and correct. To certify, the certification statement must be electronically signed and dated by an authorized official at your company. The authorized official typically is a senior official with management responsibility for the person (or persons) completing the form(s). You must include the printed name, title, and email address for the person signing the certification.

See the CDX User Guide for information on how to complete an electronic signature agreement.

This certification statement applies to all the information supplied on the form(s) for your site. The certification statements appear when the submission process has been initiated, at which time the submitter must either certify or cancel the submission process. If you are completing forms for multiple sites, one submission certification will be created and must be submitted for each site. Note that knowingly providing false or misleading information or concealing required information may be punishable by fine or imprisonment or both under TSCA section 16(b)(1).

4.2 Reporting Standard

Submitters are required to exercise certain levels of due diligence in gathering the information required by the section 8(a)(7) rule. You must report your information to the extent that the information is **known to or reasonably ascertainable by** you and your company.

The term “known to or reasonably ascertainable by” is defined in 40 CFR 705.3, meaning all information in a person’s possession or control, plus all information that a reasonable person similarly situated might be expected to possess, control, or know.

Under TSCA section 8(a), EPA may collect information associated with chemical substances to the extent that it is known to or reasonably ascertainable by the submitter. This includes, but is not limited to, information that may be possessed by employees or other agents of the company reporting under the section 8(a)(7) rule, including persons involved in the research, development, manufacturing, or marketing of a chemical substance and includes knowledge gained through discussions, symposia, and technical publications. For purposes of

section 8(a)(7), the known to or reasonably ascertainable by standard applies to all the information required by the rule.

Examples of types of information that are considered to be in a person's possession or control, or that a reasonable person similarly situated might be expected to possess, control, or know include:

- Files maintained by the manufacturer, such as marketing studies, sales reports, or customer surveys,
- Information contained in standard references, such as a safety data sheet (SDS) or a supplier notification, and
- Information from the Chemical Abstracts Service (CAS) and from Dun & Bradstreet D-U-N-S®.

The hypothetical examples in Table 4-1 illustrate the anticipated application of the "known to or reasonably ascertainable" reporting standard, in the specific context of the collection of processing and use data under section 8(a)(7). Because the standard applies on a case-by case basis, however, these examples cannot substitute for a complete analysis of a submitter's particular circumstances.

This reporting standard does not confer a testing requirement on manufacturers. But, if manufacturers have previously tested their products for the presence of PFAS, then that information may be considered known to or reasonably ascertainable to them and should be submitted to EPA as appropriate.

Table 4-1. Examples of the Application of the "Known to or Reasonably Ascertainable" Reporting Standard for Processing and Use Data

<table>
<tr><th>Scenarios, Actions, and Outcomes</th></tr>
<tr><td><u>Scenario:</u> Example Company J discovers that it has no knowledge of how a particular PFAS (Example PFAS J) is processed or used by its customers. Example Company J usually maintains marketing data documenting customers' use of its chemicals, in line with the reasonable business practices typical of comparable manufacturers, but it irrevocably lost these data for Example PFAS J due to an inadvertent computer malfunction. Example Company J has many customers, but it expects that it could substantially reconstruct this missing information by briefly contacting its largest customer and asking that customer what Example PFAS J is generally used for.

Application of KRA Reporting Standard:
<table>
<tr><th>If:</th><th>Then:</th></tr>
<tr><td>Example Company J contacts its largest customer and reports on the basis of the processing and use data that the customer was willing to provide.</td><td>Duties Likely Fulfilled</td></tr>
<tr><td>Example Company J did not endeavor to supplement the information it already knew.</td><td>Duties Not Fulfilled</td></tr>
</table>
</td></tr>
</table>

Scenario: Example Company K has never maintained information on how a particular PFAS (PFAS K) is processed or used by its customers. However, it is typical for comparable manufacturers to collect such information as part of their reasonable business practices. Example Company K has many customers, who it believes process and use the particular PFAS in a similar manner and it expects that it could substantially fill this data gap by reviewing the public website of its largest customer.

Application of KRA Reporting Standard:

If:	**Then:**
Example Company K reviews its largest customer's website, and of the information contained on the website	Duties Likely Fulfilled
Example Company K did not endeavor to supplement the information it already knew.	Duties Not Fulfilled

Scenario: Example Company L maintains seasonal marketing data on changes in use patterns for a particular PFAS (Example PFAS L). Comparable manufacturers typically only maintain such data on an annual basis, in line with reasonable business practices. Example Company L irrevocably loses its summer marketing data for Example PFAS L, due to an inadvertent computer malfunction. Example Company L expects that it could substantially reconstruct the missing summer marketing data by contacting its largest customer and asking the customer what it used or processed Example PFAS L for in the past summer.

Application of KRA Reporting Standard:

If:	**Then:**
Instead of attempting to reconstruct the summer data by contacting its largest customer, Example Company L reports on the basis of the processing and use data that it already knows (regarding the winter, spring, and fall of the year).	Duties Likely Fulfilled
Example Company L designated the information as "not known or reasonably ascertainable" simply because one of the seasonal marketing reports was missing	Duties Not Fulfilled

Scenario: Example Company M has never maintained information on how a particular PFAS (Example PFAS M) is processed or used by its customers. However, it is typical for comparable manufacturers to collect such information as part of their reasonable business practices. Example Company M has one major customer and ten minor customers.

Application of KRA Reporting Standard:

If:	**Then:**
Example Company M asks its major customer to supply information about how Example PFAS M is processed and used, but that customer is unwilling to supply this information. Example Company M reasonably expects that the only remaining way to substantially fill this data gap would be to send a survey to its ten minor customers. Example Company M reports that the information is "not known or reasonably ascertainable" to it.	Duties Likely Fulfilled
Example Company M did not endeavor to obtain processing and use information from its customers and	Duties Not Fulfilled

designated the information as "not known or reasonably ascertainable."	

Scenario: Example Company N imports an article with a water repellant "fluoropolymer" surface. However, Example Company N does not know the chemical identity or molecular structure of the fluoropolymer coating.

Application of KRA Reporting Standard:

If:	**Then:**
Example Company N contacts their supplier to determine the name, CASRN, and molecular structure of the fluoropolymer. The supplier provides this information or a joint submission is initiated.	Duties Likely Fulfilled
Example Company N did not contact their supplier to obtain information on the fluoropolymer coating	Duties Not Fulfilled

Scenario: Example Company O imports stain-resistant garments. Example Company O does not know specifically what chemical is used to impart stain resistance, but Example Company O does know that chemicals used to impart stain resistance are often fluorinated chemicals and could meet the definition of PFAS.

Application of KRA Reporting Standard:

If:	**Then:**
Example Company O contacts their supplier to determine the name, CASRN, and molecular structure of the stain-resistant chemical. The supplier provides this information or a joint submission is initiated.	Duties Likely Fulfilled
Example Company O did not contact their supplier to obtain Duties Not Fulfilled information on the stain-resistant chemical.	Duties Not Fulfilled

4.3 Part I - Section A. Parent Company Information[4]

You must provide information about your parent company. For purposes of section 8(a)(7), a parent company is the highest-level company of your site's ownership hierarchy as of the start of the submission period according to the definitions of *parent company* and *highest-level parent company* at 40 CFR 711.3. Report your highest-level parent company located in the United States. Provide the company name, address, and D&B number following the instructions, including the naming conventions, provided below. Table 4-2 contains examples of how to identify the parent company in different situations.

Note that although CDR requires you to report your U.S. parent company and your foreign parent company, section 8(a)(7) reporting requires only the U.S. parent to be reported.

[4] See Section 4.4.1 for information concerning CBI claims for Parent Company Information.

Table 4-2. Applying Highest-level Parent Company Definition in Different Situations

Site Ownership	*U.S. Parent Company*
(1) If the site is entirely owned by a single U.S. company that is not owned by another company	Then that single company is the U.S. parent company.
(2) If the site is entirely owned by a single U.S. company that is, itself, owned by another U.S.-based company (e.g., it is a division or subsidiary of a higher- level company)	The highest-level domestic company in the ownership hierarchy is the U.S. parent company.
(3) If the site is owned by more than one company (e.g., company A owns 40 percent, company B owns 35 percent, and company C owns 25 percent of the site)	The company with the largest ownership interest in the site is the parent company. Under this scenario, this would be either company A itself (if it doesn't have a U.S.-based parent company), company A's parent, or, if it exists, a single parent company that owns both company B and company C, in which case that single parent company would have the largest ownership interest (e.g., corporation X owns companies B and C, for a total ownership of 60 percent for the site). If the parent company is a U.S. company owned by another U.S. company, then the highest-level domestic company in the ownership hierarchy is the U.S. parent company. If the parent company is a foreign company, then the site is its own U.S. parent company.
(4) If the site is ultimately owned by a 50:50 joint venture or a cooperative	The joint venture or cooperative is its own U.S. parent company.
	If the site is owned by a U.S. joint venture or cooperative, the highest level of the joint venture or cooperative is the U.S. parent company.
(5) If the site is entirely owned by a foreign company (i.e., without a U.S.-based subsidiary within the site's ownership hierarchy)	The site is the U.S. parent company.
(6) If the site is a federally owned site	The highest-level federal agency or department is the U.S. parent company.
(7) If the site is owned by a non-federal public entity	That entity (such as a municipality, State, or tribe) is the U.S. parent company.

4.3.1 U.S. Parent Company Name(s)

All sites must enter the full name of the U.S. parent company. EPA requires that parent companies be referenced consistently by the same name so that site-level information can be aggregated to the associated parent company. This can be challenging because filers within the same parent company often submit names with small variations (e.g., Exopack vs. Exopack Holdings Corp). When reporting your parent company name, eliminate all periods, commas,

and all leading, trailing, and duplicate spaces. Replace commonly used acronyms and corporate terms according to Table 4-3.

Table 4-3. Parent Company Name Standardization

Use This	Not This
&	AND
CORP	CORPORATION
ASSOC	ASSOCIATION
CO	COMPANY
COS	COMPANIES
DIV	DIVISION
INC	INCORP
INC	INCORP.
INC	INCORPORATED
INC	INCORPERATED
LP	LIMITED PARTNERSHIP
LTD	LIMITED
LLC	LIMITED LIABILITY COMPANY
LLC	LIMITED LIABILITY CO.
PTNR	PARTNERSHIP
USA	U.S.A.
USA	U.S.A
USA	U S A
USA	UNITED STATES OF AMERICA
USA	UNITED STATES

4.3.2 Parent Company Dun & Bradstreet D-U-N-S® Number

Enter the 9-digit Dun & Bradstreet D-U-N-S® number (D&B number) associated with each parent company name. The number may be obtained from the treasurer or financial officer of the company.

D&B assigns separate numbers to subsidiaries and parent companies; you should make sure that the number you provide EPA belongs to your U.S. parent company. To verify the accuracy of your site and parent company D&B number and name, go to

www.dnb.com/product/dlw/form_cc4.htm or call 1-800-234-3867. Callers to the toll-free phone number should understand that the D&B support representatives will need to verify that callers requesting the D&B number are an agent of the business. D&B recommends knowing basic information such as when the business originated, officer names, and the name, address, and phone number for the site.

For the purpose of responding to the section 8(a)(7) rule, you are ***not*** required to obtain a D&B number for your parent company if none exists. However, if your parent company does not have a D&B number, you can request one from your local office of D&B if desired. There is no charge for this service, and you are not required to disclose sensitive financial information to get a number. For more information on obtaining a D&B number, see *www.dnb.com*. If you are already listed with D&B, but do not know your number, you can call 1-800-234-3867 for assistance.

4.3.3 Parent Company Address

Enter the mailing address of each parent company, including the appropriate county or parish, using standard addressing techniques as established by the U.S. or international postal services. Post office box numbers should be accompanied by a street address. If a post office box is listed, it must be entered after the street address. Standardized conventions for listing a street address should be used to account for common formatting discrepancies, such as punctuation (by eliminating all periods, commas, and all leading, trailing, and duplicate spaces), capitalization, and abbreviations in order to increase the reliability and usability of the data. Replace commonly used acronyms and street abbreviations according to Table 4-4:

Table 4-4. Parent Company Street Address Standardization

Use This	Not This
AVE	AVENUE
AVE	AVE.
BLVD	BOULEVARD
BLVD	BLVD.
DR	DRIVE
DR	DR.
HWY	HIGHWAY
HWY	HWY.
JCT	JUNCTION
JCT	JCT.
LN	LANE
LN	LN.

PL	PLACE
PL	PL.
PO BOX	P.O. BOX
RD	ROAD
RD	RD.
RTE	ROUTE
ST	STREET
ST	ST.

4.4 Part I - Section B. Site Information

EPA requires the following information to be reported for each site at which a reportable chemical substance is manufactured: the site name, site D&B number, street address, city, county (or parish), state, and zip code, and six-digit North American Industry Classification System (NAICS) code(s) of the site.

4.4.1 Confidentiality of Company, Site, and Technical Contact Information

Check the appropriate CBI box in this block and complete the substantiation questions to assert a confidentiality claim for the link between the chemical substance and the company or site identity reported in Part I or the technical contact identity reported in Part II – Section B. Checking the CBI box automatically triggers the substantiation questions to appear later in the CBI Substantiation portion of the form. See Table 4-13Table 4-13 for substantiation questions related to these data elements. **If you do not check the CBI box for any information element, then that information is not claimed as CBI and may be made public without further notice to you.** Further, if you fail to substantiate your CBI claims in accordance with the statute and applicable rules, EPA may make the information available to the public without further notice to you. For additional information about how to answer substantiation questions, visit *www.epa.gov/tsca-cbi* on the EPA website.

You may assert a claim of confidentiality for a site, company, or technical contact identity to protect the link between that information and the reported chemical substance. Such claim may only be asserted where the linkage of that information to a reportable PFAS is confidential and not publicly available. You may claim the connection between chemical substance and company, site, or technical contact as confidential for some PFAS for which you are reporting, while not making the claim for others. Any confidentiality claims need to be made on a chemical-by-chemical basis. For example, if you claimed as confidential the link between chemical A and your company information and do not claim the link as confidential for chemical B, EPA may make the link between your company and chemical B public without notice. If the chemical identity is confidential, your company may instead claim the chemical identity as confidential to protect the link between the company, site, or technical contact

information and the chemical identity. Ensure you are claiming the correct data elements as CBI to protect confidential data.

EPA also has observed that submitters sometimes claim only their company identity, but not their site identity, as confidential. EPA will not impute the existence of a CBI claim for site identity from a CBI claim for company identity, even if the company name appears within the site identity information. In other words, if your intent is to claim company name as confidential you must claim all data elements that reference or allude to company name as CBI. The failure to do this will likely result in a denial of a CBI claim for company name.

4.4.2 Special Provisions for Certain Sites

For PFAS that are domestically manufactured, the site is the location where the PFAS is physically manufactured.

For importers, the site where you import a chemical substance is considered the site of the operating unit within your organization that is directly responsible for importing the chemical substance and that controls the import transaction. For section 8(a)(7), all importers must provide a U.S. address for the controlling site; this site may be your company's headquarters in the United States. If there is no such operating unit or headquarters in the United States, the site address for the importer is the U.S. address of an agent acting on the importer's behalf who is authorized to accept service of process for the importer (40 CFR 711.3). In the event that more than one person may meet the definition of "importer" (40 CFR 704.3), only one person should report. See 40 CFR 711.22(b).

Example 4-1. The headquarters of your company is located in New Town. Your company owns a plant site located in Old Town, which is in a different state. A headquarters employee purchases and arranges to have 50,000 lb of Example PFAS P imported from Japan to the Old Town plant site. The headquarters site in New Town controls the import transaction and is the site reported.

Example 4-2. The headquarters of your company is located in New Town. Your company owns three manufacturing sites, Sites 1, 2, and 3, all located in different states. An employee based at headquarters purchases and arranges to have 50,000 lb of Example PFAS R imported from Japan. The chemical is distributed as follows: 2,000 lb is delivered to Site 1; 18,000 lb is delivered to Site 2; and 30,000 lb is delivered to Site 3. The headquarters in New Town controls the import transaction for all three sites, and therefore is responsible for reporting all 50,000 lb of Example PFAS R. The site reported is New Town.

4.4.3 Site Name

The section 8(a)(7) reporting tool will automatically populate the site name from the site used for CDX registration. If you need to change this information, you will need to make corrections or create a new site in CDX and create a new form for the corrected or new site.

4.4.4 Site Dun & Bradstreet Number D-U-N-S®

D&B assigns separate numbers to subsidiaries and parent companies; make sure that the number you provide EPA belongs to the individual site for which you are reporting. You are ***not*** required to obtain a D&B number for the site if none exists. However, if the site does not have a D&B number, you can request one from your local office of D&B if desired. Please refer to Section 4.3.2 for information on obtaining a D&B number.

4.4.5 Site Street Address

The reporting tool will automatically populate the site address from the site used for CDX registration. If you need to change this information, you will need to make corrections or create a new site in CDX and create a new form for the corrected or new site.

4.4.6 NAICS code

Enter the appropriate six-digit North American Industry Classification System (NAICS) code or choose the correct code for each site reported. The NAICS code is the standard used by Federal statistical agencies in classifying business establishments for the purpose of collecting, analyzing, and publishing statistical data related to the U.S. business economy. Information about NAICS codes can be obtained from the U.S. Census website at *www.census.gov/eos/www/naics/*.

In some circumstances it may be challenging to identify a single NAICS code for the site. In those circumstances, you may report up to three NAICS codes to more appropriately describe your site. For example, headquarters sites that import for other sites may have difficulty identifying a single NAICS code.

4.4.7 Technical Contact Information

This section requests information about the person whom EPA may contact for clarification of the information in your submission. The technical contact should be a person who can answer questions about the reported PFAS. Typically, a person located at the manufacturing site is best able to answer such questions. However, companies may use their discretion in selecting a technical contact or multiple technical contacts, as provided by the section 8(a)(7) online reporting tool. In selecting the technical contact, submitters should consider that EPA may have follow-up questions about a PFAS data submission years after the submission date. The technical contact need not be the person who signed the certification statement.

4.4.7.1 Technical Contact Name and Company Name

Enter the name of the person whom EPA may contact for clarification of information submitted. Enter the name of the company employing the technical contact. You may use the same technical contact for all chemicals submitted or you may use a different technical contact for each chemical.

4.4.7.2 Technical Contact Telephone Number and Email Address

Enter the technical contact's telephone number, including the area code, and the contact's email address. If the technical contact is outside of the United States, include the country code.

4.5 Part II - Section A. Chemical Substance Identification

You must use the Agency's Substance Registry Services (SRS) to report the chemical substance identification information consisting of the currently correct Chemical Abstracts (CA) Index Name and the correct corresponding Chemical Abstracts Service (CAS) Registry Number (CASRN), as described in Sections 4.5.4 and4.5.6. The SRS is EPA's central system for information about chemical substances that are tracked or regulated by EPA or other sources. It is the authoritative resource for basic information about chemicals, biological organisms, and other chemical substances of interest to EPA and its state and tribal partners.

The correct CA Index Name and CASRN must be reported separately for each reportable PFAS at your site. If you wish to report a PFAS listed on the confidential portion of the TSCA Inventory, you will need to report the PFAS using a TSCA Accession Number (the generic chemical name corresponding to the Accession Number will automatically be incorporated into your form). See Section 4.5.1 for details on how to report confidential chemical substances. If you have a low-volume exemption (LVE) case number for the chemical substance, that number may be used if a CASRN or Accession Number is not known to or reasonably ascertainable by you. If you know the CASRN or Accession Number for the chemical substance, report that number instead of an LVE case number.

You will be able to connect directly to the SRS database from the reporting tool to report the correct CA Index Names and CASRNs for all of your non-confidential chemical substances on the TSCA Inventory. TSCA Accession Numbers and generic chemical names will be listed instead of CA Index Names and CASRNs for chemical substances on the confidential portion of the TSCA Inventory. The use of the SRS to obtain the identities for all reportable chemical substances is a convenient way to meet the chemical nomenclature requirement and will help to prevent errors in the reporting of chemical identification information for section 8(a)(7).

> ***Duplicative Reporting***
> The information in this section regarding physical form, described in Section 4.5.12, may have been previously reported under CDR. See Section 1.2 for instructions on how to inform EPA that this information has already been reported.

If certain information in section A is not known to or reasonably ascertainable by you (including your company), you may enter or select "NKRA" for "not known or reasonably ascertainable" in the box corresponding to that data element. You may only report NKRA in this section for the chemical ID, molecular structure, or physical state of the PFAS. You **may not** report NKRA for the specific or generic chemical name or trade or common name.

4.5.1 Confidentiality of Chemical Substance Information

If you wish to report a chemical substance listed on the confidential portion of the TSCA Inventory, you will need to report the chemical substance using a TSCA Accession Number.

Accession numbers are only assigned to inventory chemicals and not to other chemicals authorized to be in US commerce, like LVEs. The generic chemical name corresponding to the TSCA Accession Number will also be automatically incorporated into your report.

The identities of chemical substances listed on the public version of the TSCA Inventory are already publicly known. Therefore, claims for confidential treatment of the identity of a chemical substance which is listed on the public section of the TSCA Inventory are not valid and will not be allowed (40 CFR 715.30(a)(2)(i)). This includes claims for confidential treatment of the chemical name, ID, and molecular structure.

You may claim as confidential the identity (chemical name, CAS registry number, and molecular structure) of a chemical substance that is already listed as confidential on the TSCA Inventory (40 CFR 715.30(c)). To do so, you must check the appropriate CBI box and submit detailed written answers to the substantiation questions listed in Table 4-5. The confidentiality claim is only applicable to the information as it is listed on the confidential portion of the TSCA Inventory; the corresponding accession number and generic chemical name listed on the public portion of the TSCA Inventory is already public and cannot be claimed as confidential. You may also claim as confidential the identity of a chemical substance that is not listed on the TSCA Inventory, e.g., LVE substances. CBI claims for trade names or common names are allowed but may not be valid if the trade name or common name is public.

CBI claims for physical state(s) of the chemical are allowed regardless of the confidentiality status of the chemical. Substantiation questions to be answered for physical state CBI claims are the same questions to be answered for confidentiality of manufacturing information listed in Table 4-13Table 4-13 in Section 4.7.1.2

CBI claims for chemical identity will be accepted only when accompanied by a separate written substantiation for the chemical substances claimed as CBI, except for chemicals reported on article importer forms. Article importers are not required to assert CBI claims for chemical identity. Additionally, PFAS manufacturers (except article importers) who do not know nor can reasonably ascertain one of the following chemical-specific identifiers, are not required to assert and substantiate a CBI claim for the PFAS identity: CASRN, TSCA Accession number, or LVE number. Checking the CBI box automatically triggers the substantiation questions to appear later in the CBI Substantiation portion of the form. If you fail to click the checkbox next to "CBI

for Chemical Identification" or fail to substantiate the claim for confidentiality of the chemical identity in accordance with applicable rules, EPA may make the information available to the public. Note that checking this box does not protect the link between your company and the chemical substance; it only asserts a CBI claim for the specific identity of the chemical substance as listed on the confidential portion of the TSCA Inventory.

Following the conclusion of the reporting period for this rule, EPA intends to compile a list of reported confidential Inventory substances for which either no chemical identity CBI claim was asserted or for which the claim was denied. Similar to past compilations, EPA will publish this list of candidates for disclosure on the public version of the Inventory, by TSCA accession number, on the EPA website for several months in advance of any update to the Inventory itself. Interested parties will have an opportunity to review the list for possible errors and contact EPA with any questions or concerns about specific candidates. In some cases, there may be assertions by a company that a mistake has been made (e.g., an incorrect chemical was reported), in which case EPA will undertake appropriate factual investigation as necessary to confirm whether there were any errors that would cause EPA to reconsider whether the chemical is no longer entitled to confidential Inventory protection. This investigation would take place prior to the point that the specific chemical identity would be disclosed on the public Inventory.

The requirements to report by Accession number, assert a CBI claim, and to substantiate such claims to maintain confidential Inventory treatment **do not apply** to submissions concerning imported articles. Such reporters may assert a CBI claim for trade name (if not already public) or other non-public identifiers, but need not report by Accession number or assert a CBI claim to maintain the confidential status of any chemical(s) associated with the trade name or generic chemical name. EPA will not determine the CBI status of a chemical identity based on imported article reporting.

Additional information about making and substantiating confidentiality claims is available on EPA's website, at *www.epa.gov/tsca-cbi*.

Table 4-5. Substantiation Questions to be Answered when Asserting Chemical Identity CBI Claims (40 CFR 705.30(e))

No.	Question
1.	Please specifically explain what harm to the competitive position of your business would be likely to result from the release of the information claimed as confidential. How would that harm be substantial? Why is the substantial harm to your competitive position likely (i.e., probable) to be caused by release of the information rather than just possible? If you claimed multiple types of information to be confidential (e.g., site information, exposure information, environmental release information, etc.), explain how disclosure of each type of information would be likely to cause substantial harm to the competitive position of your business.

No.	Question
2.	Has your business taken precautions to protect the confidentiality of the disclosed information? If yes, please explain and identify the specific measures, including but not limited to internal controls, that your business has taken to protect the information claimed as confidential. If the same or similar information was previously reported to EPA as non-confidential (such as in an earlier version of this submission), please explain the circumstances of that prior submission and reasons for believing the information is nonetheless still confidential.
3.	(i) Is any of the information claimed as confidential required to be publicly disclosed under any other Federal law? If yes, please explain. (ii) Does any of the information claimed as confidential otherwise appear in any public documents, including (but not limited to) safety data sheets; advertising or promotional material; professional or trade publications; state, local, or Federal agency files; or any other media or publications available to the general public? If yes, please explain why the information should be treated as confidential.
4.	Is the claim of confidentiality intended to last less than 10 years (see TSCA section 14(e)(1)(B))? If yes, please indicate the number of years (between 1–10 years) or the specific date after which the claim is withdrawn.
5.	Has EPA, another federal agency, or court made any confidentiality determination regarding information associated with this chemical substance? If yes, please provide the circumstances associated with the prior determination, whether the information was found to be entitled to confidential treatment, the entity that made the decision, and the date of the determination.
6.	Is this chemical substance publicly known (including by your competitors) to be in U.S. commerce? If yes, please explain why the specific chemical identity should still be afforded confidential status (*e.g.*, the chemical substance is publicly known only as being distributed in commerce for research and development purposes, but no other information about the current commercial distribution of the chemical substance in the United States is publicly available). If no, please complete the certification statement: I certify that on the date referenced, I searched the internet for the chemical substance identity (*i.e.*, by both chemical substance name and CASRN). I did not find a reference to this chemical substance that would indicate that the chemical is being manufactured or imported by anyone for a commercial purpose in the United States. [provide date].
7.	Does this particular chemical substance leave the site of manufacture (including import) in any form, *e.g.,* as a product, effluent, emission? If yes, please explain what measures have been taken to guard against the discovery of its identity.
8.	If the chemical substance leaves the site in a form that is available to the public or your competitors, can the chemical identity be readily discovered by analysis of the substance (*e.g.*, product, effluent, emission), in light of existing technologies and any costs, difficulties, or limitations associated with such technologies? Please explain why or why not.
9.	Would disclosure of the specific chemical name release confidential process information? If yes, please explain.

4.5.2 Are you manufacturing a mixture or a chemical substance of unknown or variable composition or a polymer?

You should report for PFAS that are chemical substances as defined by TSCA. Note that a mixture is not considered a chemical substance. ***Mixture*** *means any combination of two or more chemical substances if the combination does not occur in nature and is not, in whole or in part, the result of a chemical reaction; except that such term does include any combination which occurs, in whole or in part, as a result of a chemical reaction if none of the chemical substances comprising the combination is a new chemical substance and if the combination could have been manufactured for commercial purposes without a chemical reaction at the time the chemical substances comprising the combination were combined. (TSCA 3(10))*

If you manufacture a mixture, you must determine whether you manufactured any components of the mixture and report for each individual PFAS component of the mixture using the information known to or reasonably ascertainable by you.

If you manufacture a PFAS as a result of a chemical reaction, you may manufacture a chemical substance of unknown or variable composition (UVCB). A UVCB substance is an indefinite combination of chemicals, that does not meet the statutory definition of "mixture" at TSCA section 3(10), whose number and individual identities and/or composition are not precisely or completely known. A UVCB combination of chemicals is subject to reporting under section 8(a)(7) and is considered a single chemical substance.

- If you imported a mixture, you will need to report the individual PFAS components of the mixture.
- If you domestically manufactured a mixture, you will need to determine whether any PFAS chemical substances were formed from a chemical reaction that occurred as part of manufacturing the mixture. If a chemical reaction has occurred, a PFAS formed from the chemical reaction may be a chemical substance subject to reporting. If a chemical reaction has not occurred, you have not manufactured any reportable chemical substances in the production of the mixture. In such a case, the production of the mixture has not triggered any requirement to report under the PFAS data call.
- Domestic manufacturers and importers should also consider whether the combination of the chemicals they have domestically manufactured or imported (respectively) should be chemically identified for TSCA purposes as a single UVCB chemical substance instead of a mixture.

EPA has developed two Inventory nomenclature guidance documents related to the mixture-UVCB determination:

- Toxic Substances Control Act Inventory Representation for Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials:

UVCB Substances. Available online at: www.epa.gov/sites/production/files/2015-05/documents/uvcb.pdf;

- Toxic Substances Control Act Inventory Representation for Combinations of Two or More Substances: Complex Reaction Products. Available online at: www.epa.gov/sites/production/files/2015-05/documents/rxnprods.pdf

Polymers are a specific type of chemical that may have unknown or variable composition. Polymers often consist of a mixture of molecules with varying degree of polymerization, so that individual polymer molecules have different chain lengths and/or branching and therefore have different molecular structures. For copolymers (polymers formed from multiple monomer species), there may also be variance in the ratio and connectivity of the monomer subunits. In that case, report the identity of each monomer and average ratios for each copolymer. A polymer should be reported as a single PFAS. Provide any known information about the structure and variability of the structure in the chemical description and molecular structure data fields.

4.5.3 How to Report when Chemical Identity is Unknown

In some cases, you may know that you are manufacturing (including importing) a PFAS but not know the identity of the PFAS. For instance, this can occur if you import a PFAS and your supplier will not disclose the identity of the chemical, or if you do not know the identity of reaction products or byproducts.

You must use all information known to or reasonably ascertainable by you to determine if you are manufacturing a PFAS. For example, if you import a type of product known to sometimes include PFAS, this could include reviewing purchase records, SDS or product data sheets, or contacting your supplier. Additionally, you may consider the generic or trade name provided by your supplier, published studies, results of testing or other analysis, or any other information known to or reasonably ascertainable by you, in determining whether you have a reportable PFAS. If you determine that the chemical substance is unlikely to be a PFAS as defined by section 8(a)(7), you are not required to report.

If you determine that the chemical substance likely meets the definition of PFAS, you must report the chemical even if you do not know its specific chemical identity. You must report a chemical ID number (i.e., CASRN, TSCA Accession number, or LVE number) if one is known to or reasonably ascertainable by you; note that CAS numbers, Accession numbers, and LVE numbers may be assigned to chemicals with unknown or variable composition. Additionally, if you know or can reasonably ascertain another entity who would be able to provide the chemical identity (e.g., a co-manufacturer or a foreign supplier), you must initiate a joint submission with that entity. See Section 4.13 for more details on joint submissions.

For the chemical name, report the CA Index name if known to or reasonably ascertainable by you. If the CA index name is not known to or reasonably ascertainable by you, provide the generic chemical name or description of the PFAS instead. If the PFAS is not on the

public portion of the TSCA Inventory, you may claim the name as CBI. Substantiation is required unless the PFAS has not been introduced into commerce (TSCA section 14(c)(2)(G)).

Provide the trade name or common name as appropriate. If the PFAS does not have a trade name or common name, report "NA." For the molecular structure, provide a correct representative or partial chemical structure diagram, as complete as can be known, if one can be reasonably ascertained. Further details on what to include in the structure diagram are provided in Section 4.5.9.

4.5.4 Chemical Substance Identifying Number

Every chemical substance reported in accordance with the section 8(a)(7) rule must be accompanied by its correct CASRN, corresponding to the chemical substance's specific chemical name as described in Section 4.5.6. (40 CFR 705.15(b)(1)(i)). You may enter either a CASRN or the specific name of the chemical substance to select the appropriate CASRN/Chemical Abstracts (CA) Index Name combination from the SRS database.

Report the correct CASRN for your chemical substance if it is listed on the non-confidential portion of the TSCA Inventory. In the case of a chemical substance listed on the confidential portion of the TSCA Inventory, report the TSCA Accession Number as the chemical identifying number. Note that the SRS contains a cross-reference list that displays the Accession Number, generic chemical name, and PMN case number (or for an initial TSCA Inventory substance, the TSCA Inventory reporting form number) for any chemical substance listed on the confidential portion of the TSCA Inventory.

PFAS are often confidential and therefore are usually assigned Accession numbers. You can look up a chemical's Accession number in SRS if you have the PMN case number. You may also submit an inventory inquiry via the CDX TSCA communications module if your rights to access this information have been validated.

If the PFAS is not listed on the TSCA Inventory, it may have a low-volume exemption (LVE) case number. Report the LVE case number as the chemical identification number. If you also know the CASRN for the PFAS, report the CASRN instead. If none of these types of identification numbers have been assigned to the chemical, or if you do not know enough information about the chemical identity to determine one of those identification numbers, report NKRA.

4.5.5 ID Code

The code corresponding to the type of identifying number you selected in the SRS will be entered. See codes in Table 4-6.

Table 4-6. ID Code for Chemical Identifying Numbers

If the Number You are Reporting is a(n)	This Code Will be Entered
TSCA Accession Number	A
CAS Registry Number	C
Low-volume exemption (LVE) Case Number	L

4.5.6 Chemical Name

Report your chemical substance using the CA Index Name currently used to list the chemical substance on the TSCA Inventory. You can identify the CA Index name by searching SRS using a CASRN, the specific name of the chemical substance, or related synonyms. In the event that a synonym is used for multiple chemical substances, you should take care to select the correct substance. In describing the chemical substance, the EPA requires Chemical Abstracts Service (CAS) chemical nomenclature be used for identification purposes when it is available.

In cases where a chemical substance is listed on the confidential portion of the TSCA Inventory, the generic chemical name will automatically be incorporated into your report when you select the Accession Number.

In order to continue to protect the confidentiality of the underlying specific chemical identification information (i.e., the CASRN and specific chemical name as listed on the confidential portion of the Inventory), you must claim the chemical identity as confidential and complete the upfront substantiation. The Accession Number and generic chemical name will remain non-confidential. Failure to identify the chemical identity as confidential waives any confidentiality claim for the chemical identity and will likely result in the transfer of the chemical substance from the confidential portion of the TSCA Inventory to the public portion of the TSCA Inventory.

If any entity reports a PFAS by specific chemical identity and does not claim the specific chemical identity as CBI, EPA expects to determine that the specific chemical identity is no longer entitled to confidential treatment. However, EPA would not make this determination where an entity attests that it does not have knowledge of the specific chemical identity. Instead, an entity that does not have knowledge of a specific chemical identity must initiate a joint submission with its supplier or other manufacturer if that entity is known. In these cases, the secondary submitter would be responsible for providing the specific chemical identity and for asserting and substantiating any CBI claims concerning the specific chemical identity. See, e.g., 40 CFR 711.15(b)(3); 711.30(c). Importers of articles using the streamlined article import form are not required to assert or substantiate CBI claims for chemical identity. Therefore, joint submissions are not required or enabled for article importers.

4.5.7 Trade Name or Common Name

Report the common or trade name(s) by which the product is sold or commonly known.

4.5.8 Generic Chemical Name or Description

If you do not know the specific identity of the chemical substance, provide a description of the substance. If you claimed CBI for the chemical name, you must provide a generic chemical name. If the chemical is on the confidential portion of the TSCA Inventory, the generic chemical name will be pre-populated from EPA's Substance Registry Service (SRS).

Generic chemical names must be sufficiently detailed to identify the reported chemical as a PFAS. Specifically, any generic chemical name reported for a PFAS that does not contain "fluor" in the name would be rejected by EPA as insufficient under TSCA section 14(c)(1)(C).

Additionally, any previously existing generic chemical names from earlier TSCA section 5 submissions for PFAS without "fluor" are insufficient. Further, even if a generic chemical name reported under the TSCA 8(a)(7) rule lacks the structural unit "fluor," the Agency will identify the chemical substance as a PFAS.

4.5.9 Molecular Structure

Upload as an attachment a representative molecular structure. This is not required if your chemical is listed as a class I substance on the TSCA inventory. If the chemical has a single defined structure, provide a complete, correct chemical structure diagram. The diagram should clearly indicate the identity of the atoms and the nature of bonds joining the atoms. Any ionic charges or stereochemistry should be shown clearly. All known stereochemical details should be provided. Carbon atoms in ring systems and their attached hydrogen atoms need not be explicitly shown. Where applicable, specify the proportions of isomers or tautomeric forms, degree of neutralization, etc.

For a substance with unknown or variable composition, provide a correct representative or partial chemical structure diagram, as complete as can be known, if one can be reasonably ascertained. The diagram should indicate the characteristic structure or variable compositional elements of the substance. For PFAS described as reaction products, as much specific detail as possible should be provided.

For polymers, provide a simple, representative structural diagram that illustrates what you know or can reasonably ascertain concerning the key structural features of the polymer molecules. For example, you could identify the linkages formed during polymerization, the functional groups present, the range and typical values for the number of repeating structural units, and the relative molar ratios of the precursors. Indicate if the repeating substructures are arranged in a nonrandom order such as in graft or block arrangements. For example:

HO-C(=O)-R-O-(C(=O)-R'-C-O-R-O)$_n$-H

3<n<10, where R may be either

$-CF_2CF_2-$ or $-CF_2CF-CF_3$

and R' may be either a 1,4-substituted benzene ring or -(CF2)-

4.5.10 Additional Information on Chemical Identity

In this free text field, provide any additional information known to or reasonably ascertainable by you regarding the identity, structure, or composition of the PFAS. This may include, but is not limited to, additional information on the composition of a UVCB chemical or descriptions of a polymer. Report any additional information that was known to or reasonably ascertainable by you at the time of the substance's manufacture. If no additional information is known to or reasonably ascertainable by you, leave this text field blank.

4.5.11 Special Provisions for Joint Submitters of Unknown Chemical Substances

You may report an alternate chemical name, and a trade name, in those instances where your supplier will not disclose to you the specific chemical name of an imported PFAS because the information is claimed confidential. In these cases, you and the supplier may report the information required in a joint submission, which is further discussed in Section 4.13 of this chapter. If you, as the importer, cannot provide the chemical name, supply a trade name or other designation to identify the proprietary chemical substance and provide the supplier's (secondary submitter's) company information. Complete as much of the section 8(a)(7) reporting as is known to or reasonably ascertainable by you. In addition, you must use the reporting tool to ask the supplier (secondary submitter) of the confidential chemical substance to directly provide EPA with the correct chemical identity (as described in Section4.5.2), in a joint submission with you. Note that if you actually know or can reasonably ascertain the specific chemical identity of the chemical, you must provide that information regardless of your supplier's confidentiality claims, rather than using a joint submission.

Your request to the supplier must include instructions for submitting chemical identity information electronically, using the reporting tool via CDX (see 40 CFR 711.35), and for clearly referencing your submission. Contact information for the supplier, a trade name or other designation for the chemical substance or mixture, and a copy of the request to the supplier must be included with your submission for the chemical substance. If your connection to your supplier's name and other contact information, including the trade name, is confidential, you must indicate so by checking the CBI box. Failing to check the CBI box may result in EPA making the information publicly available without further notice to you, the submitter.

Substantiation of this confidentiality claim is not required at the time of submission.

If the secondary submitter does not know the chemical components of a mixture supplied to you, they may ask their supplier to complete the form as a tertiary submitter. When the secondary (or tertiary, as appropriate) submitter responds to the primary submitter's

request, the secondary submitter would use the reporting software to identify the chemical substance in question.

If this information is considered confidential, the secondary (or tertiary, as appropriate) submitter must indicate so by checking the CBI box and, in the case of the chemical identity as listed on the confidential portion of the TSCA Inventory, completing the required substantiation questions (as listed in section 4.5.1 of this document). The chemical-specific function cannot be claimed as confidential (see section 4.8 of this document for more information). Failing to check the CBI box may result in EPA making the information publicly available without further notice to the submitter.

These special provisions only apply in cases where the supplier will not reveal the pertinent chemical identity to you because it is claimed confidential. In the event that you actually know the chemical identity of a chemical substance subject to section 8(a)(7) reporting, you must provide that information irrespective of a supplier's confidentiality claims.

EPA will only accept joint submissions that are submitted electronically using the reporting tool via CDX (see 40 CFR 711.35) and that clearly reference the specific section 8(a)(7) submission to which they refer. See Section 4.13 in this chapter for more information on preparing joint submissions.

In the event that the supplier is unknown or no longer exists (e.g., supplier has gone out of business without a successor entity), provide as much identifying detail as is known to you and report NKRA for the secondary submitter. In this case a joint submission will not be required.

4.5.12 Physical Form

Report all physical forms of the PFAS at the time it is reacted or as it leaves your site (40 CFR 711.15(b)(2)). For each PFAS at each site, the submitter must report as many physical forms as applicable from the following six physical forms:

- Dry powder
- Pellets or large crystals
- Water- or solvent-wet solid
- Other solid
- Gas or vapor
- Liquid

4.6 Part II – Section B. The categories of use of each such substance or mixture

The processing or use information should be reported to the extent that it is known to or reasonably ascertainable by you (40 CFR 711.15). See Section 4.2 for a discussion of this reporting standard and examples of information that may or may not be known to or reasonably ascertainable by you.

If any information is not known or reasonably ascertainable by you (including your company), enter or select "NKRA" for "not known or reasonably ascertainable" in the box corresponding to that data element. Keep in mind that you **cannot** claim an "NKRA" designation as confidential.

4.6.1 Confidentiality of Processing and Use Information

Most data elements in Section B may not be claimed as confidential. You may not claim the following data elements as confidential:

- *Certain industrial processing and use data elements.* These data elements are a general description of how the chemical is used or processed and cannot be claimed as confidential:
  - type of process or use
  - industrial sector
  - function code

- *Certain Consumer and Commercial use data elements.* These data elements are a general description of how the chemical is used and cannot be claimed as confidential:
  - product category
  - function of the chemical in the consumer or commercial product
  - whether the chemical is used in commercial or consumer products
  - whether the chemical predictably is used in children's products

In this section, you may only assert a claim of confidentiality for the maximum concentration of the chemical in any product. Checking the CBI box associated with this data element automatically triggers substantiation questions. **If you do not check the CBI box for any information element, then that information is not claimed as CBI and may be made public without further notice to you.** See Table 4-13Table 4-13 for substantiation questions to be answered when asserting CBI claims for processing and use information.

4.6.2 Industrial Processing and Use

For purposes of section 8(a)(7) reporting, an industrial use means use at a site at which one or more chemical substances or mixtures are manufactured (including imported) or processed (40 CFR 705.3).

For each PFAS manufactured (including imported), report up to ten unique combinations of the following data elements: the Type of Process or Use Operation (TPU) (described in Section 4.6.2.1), the Industrial Sector (IS) (described in Section4.6.2.2), and the Function Category (FC) (described in Section4.6.2.3) (40 CFR 705.15(c)(4)). A combination of these three data elements defines a potential exposure scenario for risk-screening and priority-setting purposes. If more than ten unique combinations apply to a chemical substance, you need only report the ten combinations for the chemical substance that cumulatively represent

the largest percentage of production volume, measured by weight. The reporting tool will allow you to enter more than ten combinations if you choose to do so.

For each of these unique combinations, you are also required to report the percentage of production volume in Section C (described in Section 4.7.2.5), and information about worker exposure in Section F (described in Section4.10.5) (40 CFR 705.15(g)). When you reach these sections, the reporting tool will populate the TPU, IS, and FC codes reported in this section.

You are required to report information that is known to or reasonably ascertainable by you concerning the industrial uses of the PFAS manufactured (including imported) at sites you control and at sites controlled by people to whom you have either directly or indirectly (including through a broker/distributor, from a customer, etc.) distributed the reportable chemical substance (40 CFR 705.15(c)(1)).

4.6.2.1 Type of Process or Use Operation

To the extent that it is known to or reasonably ascertainable by you, report the code which corresponds to the appropriate Type of Processing or Use Operation (TPU) for the particular combination of IS and FC codes. Table 4-7 shows the codes and TPUs. Note that if a chemical substance is fully reacted (i.e., reporting "PC" for the processing code), then the chemical substance is wholly consumed and further processing and use information for that chemical substance will not exist. In such a situation, there is no further downstream processing and use information to be reported for that particular type of processing or use operation under 40 CFR 705.15(c)(1). A processing or use code may be reported more than once if more than one IS and/or FC code applies to the same processing or use operation. Definitions for each code are provided in Appendix D, which may assist you in determining which code to report.

Table 4-7. Codes for Reporting Types of Industrial Processing or Use Operations

Designation	Operation
PC	Processing as a reactant.
PF	Processing—incorporation into formulation, mixture, or reaction product.
PA	Processing—incorporation into article.
PK	Processing—repackaging.
U	Use—non-incorporative activities.

4.6.2.2 Industrial Sectors

Report the code that corresponds to the appropriate Industrial Sector (IS) for all sites that receive a reportable PFAS from you either directly or indirectly (including through a broker/distributor, from a customer of yours, etc.) and that process and use the PFAS to the extent that this information is known to or reasonably ascertainable by you (40 CFR

711.15(c)(2)). Table 4-8 shows the codes and sectors. Because an industrial sector may apply to more than one processing and use scenario for a chemical substance, the same IS code may be reported with different combinations of FC and TPU codes. A list identifying the correspondence between NAICS codes and IS codes is provided in Appendix D (Table D-2). Additional, more detailed information can be found on the CDR website at *www.epa.gov/cdr*. (The IS codes used for PFAS section 8(a)(7) reporting are the same as CDR IS codes).

When you chose the IS "Other," you also need to provide a written description of the use of the chemical substance. The written description should be used to provide a description at a comparable level of specificity as found with the current codes. It should not be used to add additional, more specific detail. Your description may include the NAICS code. If you select the IS "Other," a text box will appear for you to enter the description.

Table 4-8. Codes for Reporting Industrial Sectors

Code	Sector description
IS1	Agriculture, forestry, fishing, and hunting.
IS2	Oil and gas drilling, extraction, and support activities.
IS3	Mining (except oil and gas) and support activities.
IS4	Utilities.
IS5	Construction.
IS6	Food, beverage, and tobacco product manufacturing.
IS7	Textiles, apparel, and leather manufacturing.
IS8	Wood product manufacturing.
IS9	Paper manufacturing.
IS10	Printing and related support activities.
IS11	Petroleum refineries.
IS12	Asphalt paving, roofing, and coating materials manufacturing.
IS13	Petroleum lubricating oil and grease manufacturing.
IS14	All other petroleum and coal products manufacturing.
IS15	Petrochemical manufacturing.
IS16	Industrial gas manufacturing.
IS17	Synthetic dye and pigment manufacturing.
IS18	Carbon black manufacturing.
IS19	All other basic inorganic chemical manufacturing.
IS20	Cyclic crude and intermediate manufacturing.
IS21	All other basic organic chemical manufacturing.
IS22	Plastics material and resin manufacturing.
IS23	Synthetic rubber manufacturing.
IS24	Organic fiber manufacturing.
IS25	Pesticide, fertilizer, and other agricultural chemical manufacturing.
IS26	Pharmaceutical and medicine manufacturing.
IS27	Paint and coating manufacturing.
IS28	Adhesive manufacturing.

Code	Sector description
IS29	Soap, cleaning compound, and toilet preparation manufacturing.
IS30	Printing ink manufacturing.
IS31	Explosives manufacturing.
IS32	Custom compounding of purchased resins.
IS33	Photographic film, paper, plate, and chemical manufacturing.
IS34	All other chemical product and preparation manufacturing.
IS35	Plastics product manufacturing.
IS36	Rubber product manufacturing.
IS37	Non-metallic mineral product manufacturing (includes cement, clay, concrete, glass, gypsum, lime, and other non-metallic mineral product manufacturing)
IS38	Primary metal manufacturing.
IS39	Fabricated metal product manufacturing.
IS40	Machinery manufacturing.
IS41	Computer and electronic product manufacturing.
IS42	Electrical equipment, appliance, and component manufacturing.
IS43	Transportation equipment manufacturing.
IS44	Furniture and related product manufacturing.
IS45	Miscellaneous manufacturing.
IS46	Wholesale and retail trade.
IS47	Services.
IS48	Other (requires additional information).

4.6.2.3 Function Category

Report the code that corresponds to the appropriate Industrial Function Category (FC) for each particular combination of TPU and IS that you report (40 CFR 711.15(c)(3)). You must use the codes in Table 4-9 for reporting under this data call. These codes, based on Organisation for Economic Cooperation and Development (OECD) standards, were required for reporting of chemical substances designated by EPA as a high priority for risk evaluation for 2020 CDR reporting and were optional for the 2020 CDR for other chemical substances; if you reported to 2020 CDR, you may be familiar with these codes. If your site reported this PFAS to 2020 or earlier CDR using other codes, you will need to determine the appropriate 2020 CDR codes and report those in this section. Because data reported using other codes was not reported as required by the PFAS section 8(a)(7) rule, it is not considered duplicative. Descriptions for each FC and a crosswalk between the OECD-based 2020 CDR codes and 2016 CDR codes are provided in Appendix D (Table D-4Table D-4). This crosswalk may be helpful if you are already familiar with the 2016 CDR codes and can help you determine the correct 2020 CDR codes to use if you have previously reported the PFAS using 2016 CDR codes. Function Category codes to be used for section 8(a)(7) reporting are provided in Table 4-9.

If you select F999 (Other), you must provide a description of the function of the chemical substance. The written description should be used to provide a description at a comparable

level of specificity as found with the current codes. It should not be used to add additional, more specific detail.

Function codes are based on the intended physical or chemical characteristic for when a chemical substance or mixture is consumed as a reactant; incorporated into a formulation, mixture, reaction product, or article; repackaged; or used (e.g., as an abrasive, a catalyst, or an elasticizer). However, the functional use categories for consumer or commercial categories cover the life cycle and describe the specific function that a chemical provides when used in the formulation of a product or article, or when used within an industrial process. While the function of a chemical may be the same across its life cycle, certain functions may only be appropriate for consideration in an industrial setting, while others may be relevant for a consumer or commercial setting. For more information on reporting consumer and commercial use data, see Section 4.6.3 below.

Table 4-9. Codes for Reporting Function Categories

Code	Category
F001	Abrasives
F002	Etching agent
F003	Adhesion/cohesion promoter
F004	Binder
F005	Flux agent
F006	Sealant (barrier)
F007	Absorbent
F008	Adsorbent
F009	Dehydrating agent (desiccant)
F010	Drier
F011	Humectant
F012	Soil amendments (fertilizers)
F013	Anti-adhesive/cohesive
F014	Dusting agent
F015	Bleaching agent
F016	Brightener
F017	Anti-scaling agent
F018	Corrosion inhibitor
F019	Dye
F020	Fixing agent (mordant)
F021	Hardener
F022	Filler
F023	Anti-static agent
F024	Softener and conditioner

Code	Category
F025	Swelling agent
F026	Tanning agents not otherwise specified
F027	Waterproofing agent
F028	Wrinkle resisting agent
F029	Flame retardant
F030	Fuel agents
F031	Fuel
F032	Heat transferring agent
F033	Hydraulic fluids
F034	Insulators
F035	Refrigerants
F036	Anti-freeze agent
F037	Intermediate
F038	Monomers
F039	Ion exchange agent
F040	Anti-slip agent
F041	Lubricating agent
F042	Deodorizer
F043	Fragrance
F044	Oxidizing agent
F045	Reducing agent
F046	Photosensitive agent
F047	Photosensitizers
F048	Semiconductor and photovoltaic agent
F049	UV stabilizer
F050	Opacifer
F051	Pigment
F052	Plasticizer
F053	Plating agent
F054	Catalyst
F055	Chain transfer agent
F056	Chemical reaction regulator
F057	Crystal growth modifiers (nucleating agents)
F058	Polymerization promoter
F059	Terminator/Blocker
F060	Processing aids, specific to petroleum production
F061	Antioxidant

Code	Category
F062	Chelating agent
F063	Defoamer
F064	pH regulating agent
F065	Processing aids not otherwise specified
F066	Energy Releasers (explosives, motive propellant)
F067	Foamant
F068	Propellants, non-motive (blowing agents)
F069	Cloud-point depressant
F070	Flocculating agent
F071	Flotation agent
F072	Solids separation (precipitating) agent, not otherwise specified
F073	Cleaning agent
F074	Diluent
F075	Solvent
F076	Surfactant (surface active agent)
F077	Emulsifier
F078	Thickening agent
F079	Viscosity modifiers
F080	Laboratory chemicals
F081	Dispersing agent
F082	Freeze-thaw additive
F083	Surface modifier
F084	Wetting agent (non-aqueous)
F085	Aerating and deaerating agents
F086	Explosion inhibitor
F087	Fire extinguishing agent
F088	Flavoring and nutrient
F089	Anti-redeposition agent
F090	Anti-stain agent
F091	Anti-streaking agent
F092	Conductive agent
F093	Incandescent agent
F094	Magnetic element
F095	Anti-condensation agent
F096	Coalescing agent
F097	Film former
F098	Demulsifier

Code	Category
F099	Stabilizing agent
F100	Alloys
F101	Density modifier
F102	Elasticizer
F103	Flow promoter
F104	Sizing agent
F105	Solubility enhancer
F106	Vapor pressure modifiers
F107	Embalming agent
F108	Heat stabilizer
F109	Preservative
F110	Anti-caking agent
F111	Deflocculant
F112	Dust suppressant
F113	Impregnation agent
F114	Leaching agent
F115	Tracer
F116	X-ray absorber
F999	Other

4.6.3 Consumer and Commercial Use

For purposes of section 8(a)(7) reporting, a commercial use means the use of a chemical substance or a mixture (including as part of an article) in a commercial enterprise providing saleable goods or a service (40 CFR 711.3). A consumer use, on the other hand, means the use of a chemical substance or a mixture (including as part of an article) when sold to or made available to consumers for their use (40 CFR 711.3).

For each PFAS manufactured (including imported), report up to ten unique combinations of the following data elements: the Product Category (PC) (described in Section4.6.3.1), the Function Category (FC) (described in Section4.6.3.2), whether the use is consumer and/or commercial (described in Section4.6.3.3), and whether the use is in products intended for use by children (described in Section4.6.3.4) (40 CFR 705.15(c)(7)). A combination of these four data elements defines a potential exposure scenario for risk-screening and priority-setting purposes. If more than ten unique combinations apply to a chemical substance, you need only report the ten combinations for the chemical substance that cumulatively represent the largest percentage of production volume, measured by weight (40 CFR 705.15(c)(4)). The reporting tool will allow you to enter more than ten combinations if you choose to do so.

For each of these unique combinations, you are also required to report the maximum concentration (described in Section4.6.3.5), the percentage of production volume (reported in Section C of the reporting form – described in Section4.7.2.6), and, for commercial uses, information about worker exposure (reported in section C of the reporting form – described in Section4.10.7) (40 CFR 711.15(c)(8)).

You are required to report information that is known to or reasonably ascertainable by you concerning the consumer and commercial end uses of each chemical substance manufactured (including imported) at sites you control and at sites controlled by people to whom you have either directly or indirectly (including through a broker/distributor, from a customer, etc.) distributed the reportable PFAS (40 CFR 711.15(c)(4)).

4.6.3.1 Product Category

You must designate up to ten product categories which correspond to the actual use of the chemical substance by reporting the codes which correspond to the appropriate product categories (40 CFR 711.15(c)(4)). If more than ten codes apply, you need report only the ten codes for the chemical substance that cumulatively represent the largest percentage of production volume, measured by weight (40 CFR 711.15(c)(4)). The reporting tool will allow you to enter more than ten categories if you choose to do so.

You must use the codes in Table 4-10Table 4-10 for reporting under this data call. These codes, based on OECD standards, were required for reporting of chemical substances designated by EPA as a high priority for risk evaluation for 2020 CDR reporting and were optional for the 2020 CDR for other chemical substances; if you reported to 2020 CDR, you may be familiar with these codes. If your site reported this PFAS to 2020 or earlier CDR using other codes, you will need to determine the appropriate 2020 CDR codes and report those in this section. Because data reported using other codes was not reported as required by the PFAS section 8(a)(7) rule, it is not considered duplicative. Descriptions for each product category code and a crosswalk between the OECD-based 2020 CDR codes and 2016 CDR codes are provided in Appendix D (Table D-3Table D-3).

This crosswalk may be helpful if you are already familiar with the 2016 CDR codes and can help you determine the correct 2020 CDR codes to use if you have previously reported the PFAS using 2016 CDR codes. Product Category codes are provided in Table 4-10.

If you select CC980 (Other), you must provide a description of the product category. The written description should be used to provide a description at a comparable level of specificity as found with the current codes. It should not be used to add additional, more specific detail.

Table 4-10. Product Category Codes

Code	Category
Chemical Substances in Furnishing, Cleaning, Treatment Care Products	
CC101	Construction and building materials covering large surface areas including stone, plaster, cement, glass and ceramic articles; fabrics, textiles, and apparel
CC102	Furniture & furnishings including plastic articles (soft); leather articles
CC103	Furniture & furnishings including stone, plaster, cement, glass and ceramic articles; metal articles; or rubber articles
CC104	Leather conditioner
CC105	Leather tanning, dye, finishing, impregnation and care products
CC106	Textile (fabric) dyes
CC107	Textile finishing and impregnating/surface treatment products
CC108	All-purpose foam spray cleaner
CC109	All-purpose liquid cleaner/polish
CC110	All-purpose liquid spray cleaner
CC111	All-purpose waxes and polishes
CC112	Appliance cleaners
CC113	Drain and toilet cleaners (liquid)
CC114	Powder cleaners (floors)
CC115	Powder cleaners (porcelain)
CC116	Dishwashing detergent (liquid/gel)
CC117	Dishwashing detergent (unit dose/granule)
CC118	Dishwashing detergent liquid (hand-wash)
CC119	Dry cleaning and associated products
CC120	Fabric enhancers
CC121	Laundry detergent (unit-dose/granule)
CC122	Laundry detergent (liquid)
CC123	Stain removers
CC124	Ion exchangers
CC125	Liquid water treatment products
CC126	Solid/Powder water treatment products
CC127	Liquid body soap
CC128	Liquid hand soap
CC129	Solid bar soap

Code	Category
CC130	Air fresheners for motor vehicles
CC131	Continuous action air fresheners
CC132	Instant action air fresheners
CC133	Anti-static spray
CC134	Apparel finishing, and impregnating/surface treatment products
CC135	Insect repellent treatment
CC136	Pre-market waxes, stains, and polishes applied to footwear
CC137	Post-market waxes, and polishes applied to footwear (shoe polish)
CC138	Waterproofing and water-resistant sprays
Chemical Substances in Construction, Paint, Electrical, and Metal Products	
CC201	Fillers and putties
CC202	Hot-melt adhesives
CC203	One-component caulks
CC204	Solder
CC205	Single-component glues and adhesives
CC206	Two-component caulks
CC207	Two-component glues and adhesives
CC208	Adhesive/Caulk removers
CC209	Aerosol spray paints
CC210	Lacquers, stains, varnishes and floor finishes
CC211	Paint strippers/removers
CC212	Powder coatings
CC213	Radiation curable coatings
CC214	Solvent-based paint
CC215	Thinners
CC216	Water-based paint
CC217	Construction and building materials covering large surface areas, including wood articles
CC218	Construction and building materials covering large surface areas, including paper articles; metal articles; stone, plaster, cement, glass and ceramic articles
CC219	Machinery, mechanical appliances, electrical/electronic articles
CC220	Other machinery, mechanical appliances, electronic/electronic articles
CC221	Construction and building materials covering large surface areas, including metal articles
CC222	Electrical batteries and accumulators

Code	Category
Chemical Substances in Packaging, Paper, Plastic, Toys, Hobby Products	
CC990	Non-TSCA use
CC301	Packaging (excluding food packaging), including paper articles
CC302	Other articles with routine direct contact during normal use, including paper articles
CC303	Packaging (excluding food packaging), including rubber articles; plastic articles (hard); plastic articles (soft)
CC304	Other articles with routine direct contact during normal use including rubber articles; plastic articles (hard)
CC305	Toys intended for children's use (and child dedicated articles), including fabrics, textiles, and apparel; or plastic articles (hard)
CC306	Adhesives applied at elevated temperatures
CC307	Cement/concrete
CC308	Crafting glue
CC309	Crafting paint (applied to body)
CC310	Crafting paint (applied to craft)
CC311	Fixatives and finishing spray coatings
CC312	Modelling clay
CC313	Correction fluid/tape
CC314	Inks in writing equipment (liquid)
CC315	Inks used for stamps
CC316	Toner/Printer cartridge
CC317	Liquid photographic processing solutions
Chemical Substances in Automotive, Fuel, Agriculture, Outdoor Use Products	
CC401	Exterior car washes and soaps
CC402	Exterior car waxes, polishes, and coatings
CC403	Interior car care
CC404	Touch up auto paint
CC405	Degreasers
CC406	Liquid lubricants and greases
CC407	Paste lubricants and greases
CC408	Spray lubricants and greases
CC409	Anti-freeze liquids
CC410	De-icing liquids
CC411	De-icing solids

Code	Category
CC412	Lock de-icers/releasers
CC413	Cooking and heating fuels
CC414	Fuel additives
CC415	Vehicular or appliance fuels
CC416	Explosive materials
CC417	Agricultural non-pesticidal products
CC418	Lawn and garden care products
Chemical Substances in Products not Described by Other Codes	
CC980	Other (specify)
CC990	Non-TSCA use

4.6.3.2 Functional Use for Consumer and/or Commercial Products

For each consumer and/or commercial product category reported, report the code(s) that designates the function category(ies) that best represents the specific manner in which the chemical substance is used (40 CFR 705.15(c)(5)). You must use the codes in Table 4-9Table 4-9 for reporting under this data call. These codes are the same as those used to report the appropriate Function Category for industrial processing and use. A particular function category may need to be reported more than once, to the extent that more than one consumer or commercial product category applies to a given function category.

For the special situation where the PFAS has multiple functions within the same product, you can report in one of two ways:

If one function is predominant, simply report the primary function; or

If all functions represent a substantial portion of the product, report each on a separate line and either estimate the portions individually or bifurcate the percent Production Volume (%PV) equally across the functions (so as not to double or triple-count the %PV for the one product).

If none of the listed function categories accurately describes a use of a chemical substance, the category “Other” may be used, and must include a description of the use. The written description should be used to provide a description at a comparable level of specificity as found with the current codes. It should not be used to add additional, more specific detail.

4.6.3.3 Consumer and/or Commercial Use

For each product category reported, report whether the use is a consumer use or a commercial use (40 CFR 705.15(c)(4). If the product has both consumer and commercial uses, report both.

4.6.3.4 Use in Product(s) Intended for Use by Children

Within each consumer product category reported, you must determine whether any amount of each reportable chemical substance manufactured (including imported) by you is present in or on any consumer product(s) intended for use by children age 14 or younger, regardless of the concentration of the chemical substance remaining in or on the product (40 CFR 705.15(c)(7)). If you determine that your chemical substance or mixture is used in a consumer product intended for use by children, report "Yes" in the "Used in Product(s) Intended for Children" column in Part II.D.2 of the reporting form. If you determine that your chemical substance or mixture is not used in a consumer product intended for use by children, report "No."

EPA defines "intended for use by children" to mean the chemical substance or mixture is used in or on a product that is specifically intended for use by children age 14 or younger (40 CFR 705.3). Your chemical substance or mixture is intended for use by children if you answer "yes" to at least one of the following questions about the product into which your chemical substance or mixture is incorporated:

- Is the product commonly recognized (i.e., by a reasonable person) as being intended for use by children age 14 or younger?
- Does the manufacturer of the product state through product labeling or other written materials that the product is intended or will be used by children age 14 or younger?
    - Is the advertising, promotion, or marketing of the product aimed at children age 14 or younger?

Table 4-11Table 4-11 illustrates some (non-exhaustive) examples of "Use in Product(s) Intended for Use by Children." For example, certain products (e.g., crayons, coloring books, diapers, and toy cars) are typically used by children age 14 or younger. If you determine that your chemical substance or mixture is used in crayons, for example, you would report "Y" for children's use for CC305.

Certain products, such as household cleaning products, automotive supplies, and lubricants, typically are not intended to be used by children age 14 or younger. As such, if you determine that your chemical substance or mixture is used in automotive care products and lubricants, for example, you would report "no" for children's use for categories CC401 and CC402.

Table 4-11. Examples of Products Intended for Use by Children

Code	Category	Examples
Chemical Substances in Furnishings, Cleanings, Treatment Care Products		
CC102	Furniture & furnishings including Plastic articles (soft); Leather articles	Child's car seat, children's sheets
CC103	Furniture & furnishings including Stone, plaster, cement, glass and ceramic articles; Metal articles; or Rubber articles	Baby cribs, changing tables
CC106	Textile (fabric) dyes	Children's clothing
CC107	Textile finishing and impregnating/surface treatment products	Children's clothing, children's sheets, child's car seat
CC127	Liquid body soap	Baby shampoo, children's bubble bath
Chemical Substances in Construction, Paint, Electrical and Metal Products		
CC219	Machinery, mechanical appliances, electrical/electronic articles	Electronic games, remote control cars
CC222	Electrical batteries and accumulators	Batteries used in toys
Chemical Substances in Packaging, Paper, Plastic, Hobby Products		
CC302	Other articles with routine direct contact during normal use, including paper articles	Diapers, baby wipes, coloring books
CC305	Toys intended for children's use (and child dedicated articles), including Fabrics, textiles, and apparel; or Plastic articles (hard)	Pacifiers, toy trucks, dolls, toy cars, wagons, action figures, balls, swing sets, slides, skates, baseball gloves, kid's rake
CC306	Adhesives applied at elevated temperatures	Craft glue for a hot glue gun
CC308	Crafting glue	Craft glue
CC309	Crafting Paint (applied to body)	Chemicals used to add color to body paint, finger paints

4.6.3.5 Maximum Concentration Code

When the chemical substance you manufacture (including import) is used in commercial or consumer products, you are required to report the estimated typical maximum concentration (measured by weight) of each chemical substance in each commercial or consumer product category reported (40 CFR 715.15(c)(8)). For each chemical substance used

in a reported commercial or consumer product, report the code that corresponds to the appropriate concentration range. Table 4-12 shows the codes and concentration ranges.

Table 4-12. Codes for Reporting Maximum Concentration

Code	Concentration Range (weight percent)
M1	Less than 1% by weight
M2	At least 1 but less than 30% by weight
M3	At least 30 but less than 60% by weight
M4	At least 60 but less than 90% by weight
M5	At least 90% by weight

4.7 Part II – Section C. Manufacturing, Processing, and Use Information

The following subsections describe the manufacturing information required to be reported for each PFAS.

4.7.1 Confidentiality of Manufacturing Information

Information reported in the manufacturing section of the section 8(a)(7) form can be claimed as confidential. For most of the data elements, upfront substantiation of the claim is required. Specifically, upfront substantiation:

- IS NOT required for the annual domestically manufactured volume, imported volume.
- IS required for all other data elements.

Summary of substantiation requirements for claims of confidentiality:

All claims of confidentiality, except for information exempt from substantiation under TSCA section 14(c)(2) such as production volume information (including domestic manufacture and import), and certain information in joint submissions, must be substantiated at the time of submission as required by TSCA section 14(c)(3).

When using the reporting tool, you will be prompted to substantiate claims where CBI substantiations are required.

For additional information about how to answer substantiation questions, visit *www.epa.gov/tsca-cbi* on the EPA website.

For information on EPA's policy of reviewing CBI claims, visit *EPA Review and Determination of CBI Claims under TSCA* on the EPA website.

4.7.1.1 Confidentiality of Production Volume Information

Check the appropriate CBI box in this block to assert a confidentiality claim for the associated production volume information (domestically manufactured volume, imported volume, or percent production volume for each consumer and commercial use) being submitted. **If you do not check the CBI box for any information element, then that information is not claimed as CBI and may be made public without further notice to you.**

Further, if you fail to assert your CBI claims in accordance with the statute and applicable rules, EPA may make the information available to the public without further notice to you.

4.7.1.2 Confidentiality of all Other Manufacturing Information

Check the appropriate CBI box in this block and complete the substantiation questions to assert a confidentiality claim for the associated information being submitted. Checking the CBI box automatically triggers the substantiation questions to appear later in the CBI Substantiation portion of the form. See Table 4-13 for substantiation questions related to these data elements. **If you do not check the CBI box for any information element, then that information is not claimed as CBI and may be made public without further notice to you.** Further, if you fail to substantiate your CBI claims in accordance with the statute and applicable rules, EPA may make the information available to the public without further notice to you. For additional information about how to answer substantiation questions, visit *www.epa.gov/tsca-cbi* on the EPA website.

Table 4-13. Substantiation Questions to be Answered when Asserting Manufacturing, Processing, and Use-Related Confidentiality Claims (40 CFR 705.30(b))

No.	Question
1	Will disclosure of the information claimed as confidential likely cause substantial harm to your business's competitive position? If you answered yes, describe the substantial harmful effects that would likely result to your competitive position if the information is disclosed, including but not limited to how a competitor could use such information and the causal relationship between the disclosure and the harmful effects.
2	Has your business taken precautions to protect the confidentiality of the disclosed information? If yes, please explain and identify the specific measures, including but not limited to internal controls, that your business has taken to protect the information claimed as confidential.
3	i. Is any of the information claimed as confidential required to be publicly disclosed under any other Federal law? If yes, please explain. ii. Does any of the information claimed as confidential otherwise appear in any public documents, including (but not limited to) safety data sheets; advertising or promotional material; professional or trade publications; state, local, or Federal agency files; or any other media or publications available to the general public? If yes, please explain why the information should be treated as confidential. iii. Does any of the information claimed as confidential appear in one or more patents or patent applications? If yes, please provide the associated patent number or patent application number (or numbers) and explain why the information should be treated as confidential.
4	Does any of the information that you are claiming as confidential constitute a trade secret? If yes, please explain how the information you are claiming as confidential constitutes a trade secret.
5	Is the claim of confidentiality intended to last less than 10 years (see TSCA section 14(e)(1)(B))? If yes, please indicate the number of years (between 1–10 years) or the specific date after which the claim is withdrawn.
6	Has EPA, another federal agency, or court made any confidentiality determination regarding information associated with this chemical substance? If yes, please provide the circumstances associated with the prior determination, whether the information was found to be entitled to confidential treatment, the entity that made the decision, and the date of the determination.

4.7.2 Reporting Manufacturing Information

This section describes the manufacturing data elements that should be reported for your PFAS for each year. If any information is not known or reasonably ascertainable by you (including your company), enter or select "NKRA" for "not known or reasonably ascertainable" in the box corresponding to that data element. You may also check the CBI box next to each data element to claim data as confidential. However, keep in mind that you **cannot** claim an "NKRA" designation as confidential.

4.7.2.1 Domestically Manufactured Production Volume

Report the volume of the chemical substance domestically manufactured at your site, in pounds. Report the quantity to at least two significant figures; it should be accurate to the extent known to or reasonably ascertainable by you. Production volumes should be reported in numeric format, without commas (e.g., 6352000). See Table 4-14Table 4-14 for examples.

4.7.2.2 Imported Production Volume

Report the volume of the chemical substance imported by your site, in pounds. Report the quantity to at least two significant figures; it should be accurate to the extent known to or reasonably ascertainable by you. You should use the same numeric format as described for the domestically manufactured production volume. Imported and domestically manufactured production volumes are reported separately for each PFAS at each site.

> ***Reporting for a chemical with multiple sources***
> If you import a PFAS from multiple sources, or domestically manufacture the PFAS through multiple processes, sum those sources together for reporting the total production volume, and consider the total amount for all other data fields.
>
> If you import or domestically manufacture a chemical and also have quantities on site that were not manufactured by your site (e.g., purchased from a domestic source), consider **only the volume manufactured (including imported) by your site** when reporting total production volume and all other data fields. Do not report on quantities of the PFAS that were not manufactured (including imported) by your site.

Note that if you import various mixtures containing PFAS, you should add all import volumes associated with each PFAS. For

instance, if you import three mixtures and each mixture contains PFAS A, then you would determine the volume of PFAS A in each mixture and report the aggregated amount. See Table 4-14 for examples.

For article importers reporting on the Article Importer form, you should report the volume of the article imported, rather than attempting to calculate the volume of the PFAS contained within the articles. You may choose to report the total weight of the PFAS-containing articles (e.g., in tons or pounds) or the quantity of the article imported (e.g., the number of vehicles). You must specify the unit of measurement for the reported production volume.

4.7.2.3 For Imported Chemical Substances, Is the Chemical Never Physically at Site?

Report whether or not your imported PFAS is physically at the reporting site. Report one of the following choices:

- ☐ Yes, the imported PFAS **is never** physically at the reporting site (e.g., if you ship the chemical substance from a foreign country directly to another location such as a warehouse, a processing or use site, or a customer's site).
- ☐ No, the imported PFAS **is** physically present at the reporting site.
- ☐ NA, not applicable because the PFAS is not imported.
- ☐ NKRA, it is not known to or reasonably ascertainable by you whether the imported PFAS is physically present at the reporting site.

4.7.2.4 Volume Directly Exported

Report the volume directly exported and not domestically processed or used, in pounds. The volume exported should not exceed the sum of the domestically manufactured and imported volumes minus volume used on site. Note that direct exporting includes sending a PFAS to a distributor who then exports it without repackaging it, even if it is relabeled. Direct exporting does not include sending a PFAS to a distributor who repackages and relabels it. The latter case would be considered a processing and use activity potentially reportable under Part II – Section B of the reporting form. Report the quantity to at least two significant figures; it should be accurate to the extent known to or reasonably ascertainable by you. You should use the same numeric format as described for domestically manufactured production volume (see section4.7.2.1). See Table 4-14 for examples.

Table 4-14. Examples of Reporting Volumes for Part II – Section C

Description	Reporting Requirement
Example Site S domestically manufactures 31,415 lb of Example PFAS S.	Example Site S should report 31,415 lb as domestically manufactured for Example PFAS S. The total production volume (i.e., the domestically manufactured volume) should be used to report all remaining information.
Example Site T domestically manufactures 15,000 lb of Example PFAS T and directly imports 15,112 lb of Example PFAS T.	Example Site T should report 15,000 lb as domestically manufactured. Because Example Site T controls the import transaction, Example Site T should also report 15,112 lb as imported for Example PFAS T. The total production volume (i.e., sum of the domestically manufactured and import volumes, 30,112 lb) should be used to report all remaining information.

Description	Reporting Requirement
Example Site U domestically manufactures 33,500 lb of Example PFAS U. Of the 33,500 lb manufactured, Example Site U directly exports 13,000 lb to a foreign customer.	Example Site U should report 33,500 lb as domestically manufactured and 13,000 lb as exported for Example PFAS U. The volume not directly exported (20,500 lb) should be used to report all remaining information.
Example Company V coordinates the import of 105,000 lb of Example PFAS V, which is imported directly to three different sites owned by Company V. Site 1 receives 41,000 lb and Sites 2 and 3 each receive 32,000 lb of Example PFAS V.	Example Company V should report 105,000 lb as imported for Example PFAS V. The total production volume (i.e., the imported volume) should be used to report all remaining information. Because the three sites controlled by Company V did not control the import transaction, the sites are not required to report the imported volumes.
Example Site W domestically manufacturers 77,000 lb, imports 22,000 lb, and exports 11,000 lb of Example PFAS W.	Example Site W should report an amount that does not exceed 88,000 lb as volume used at site for Example PFAS W, as the volume used at site should not be greater than the sum of the domestically manufactured and imported volumes minus the volume exported (77,000 lb + 22,000 lb – 11,000 lb).
Example Site X imports 20,000 lb of Example PFAS X and purchases 30,000 lb of Example PFAS X from a domestic producer.	Example Site X should report 20,000 lb as imported for Example PFAS X. The total production volume is 20,000 lb; the 30,000 lb of Example PFAS X purchased from a domestic producer is not included because Example Site X is not the manufacturer of that quantity of PFAS X (i.e., Site X neither imported nor produced those 30,000 lb). Only the 20,000 lb of PFAS X imported should be considered throughout the entire section 8(a)(7) form.

4.7.2.5 Industrial Processing and Use – Percentage of Production Volume

Report the estimated percentage of total production volume of the PFAS associated with each unique combination of industrial processing or use operation, sector, and function category (TPU, IS, and FC) as reported in Part II – Section B of the reporting form (see section4.6.2). The percentage should be accurate to the extent that it is known to or reasonably ascertainable by you. Round your estimates to the nearest 10 percent of production volume (40 CFR 711.15(d)(4)). If you would like to provide more specific percentages, please do so. Do not round a particular combination that accounts for less than five percent of the total production volume to zero percent. In such cases, you must report the percentage of production volume attributable to that combination to the nearest one percent of production volume.

How to determine your percent production volume:

1. Determine the production volume that is attributable to each unique combination of TPU, IS, and FC.
2. Determine your total production volume for the year.
   a. Add together the volume domestically manufactured and the volume imported.
   b. DO NOT subtract the volume used on-site or the volume exported.
3. Divide the volume determined in step 1 by the volume determined in step 2 and multiply by 100.

The total percentage of production volumes associated with the TPU, IS, and FC combinations may add up to more than 100 percent, given that you are reporting on distribution of a PFAS to sites in your control as well as downstream sites, some of which are not immediate purchasers from your original manufacturing site. Thus, you may "double count" quantities of the PFAS as you consider its use at multiple sites. The sum may also add to more than 100% due to rounding.

Additionally, the total percentage of production volume may add up to less than 100 percent if, for example:

- You do not know or cannot reasonably ascertain information about how all of your production volume is processed or used;
- More than 10 combinations of codes are applicable to your chemical substance;
- You export a portion of the production volume;
- A portion of the production volume is used for commercial, or consumer uses rather than industrial uses; or
- Percentages round such that they do not sum to 100% (e.g., three use combinations that each account for one-third of total use will be reported as 30% each, totaling 90%).

Table 4-15 provides examples of reporting industrial processing and use data.

Table 4-15. Examples of Reporting Industrial Processing and Use Information

Description	Reporting Requirement
Example Site Y manufactures 12,000 lb of Example PFAS Y for processing for incorporation into a mixture. All of the production is for use in industrial sector IS17 (Synthetic Dye and Pigment Manufacturing). Of the production volume, 67% (8,000 lb) is used as an anti-stain agent and 33% (4,000 lb) is used as a viscosity modifier.	On line 3.A.1 of the Form, enter PF for type of process or use, IS17 for industrial sector, F090 for FC, and 70% for production volume. On line 3.A.2 of the form, enter PF for type of process or use, IS17 for industrial sector, F079 for FC, and 30% for production volume.
Example Site Z manufactures 50,000 lb of Example PFAS Z for processing for incorporation into a mixture. All of the production is for use under	On line 3.A.1 of the form, enter PF for type of process or use, IS17 for industrial sector, F090 for FC, and 100% for production volume. On line 3.A.2

Description	Reporting Requirement
industrial sector IS17 (Synthetic Dye and Pigment Manufacturing). Of the production volume, 97% (48,500 lb) is used as an anti-stain agent and 3% (1,500 lb) is used as a viscosity modifier.	of the form, enter PF for type of process or use, IS17 for industrial sector, and F079 for FC. Because less than 10% of the production volume is used as a viscosity modifier, enter the percentage to the nearest one percent, i.e., 3%, for production volume.

4.7.2.6 Consumer and Commercial Use – Percentage of Production Volume

Report the estimated percentage of total production volume of the reportable chemical substance associated with each consumer and commercial product category as reported in Part II – Section B of the reporting form (see Section 4-274.6.3.1). The percentage should be accurate to the extent that it is known to or reasonably ascertainable by you. Round your estimates to the nearest 10 percent of production volume (40 CFR 705.15(d)(5)). If you would like to provide more specific percentages, please do so. Do not round a particular combination that accounts for less than five percent of the total production volume to zero percent. In such cases, you must report the percentage of production volume attributable to that combination to the nearest one percent of production volume.

The total percentage of production volumes associated with the product codes may add up to more than 100 percent, given that you are reporting on distribution of a chemical substance to sites in your control as well as downstream sites, some of which are not immediate purchasers from your original manufacturing site. Thus, you may "double count" quantities of the PFAS as you consider its use at multiple sites. The sum may also add to more than 100% due to rounding.

How to determine your percent production volume:

1. Determine the production volume that is attributable to each consumer or commercial product category.
2. Determine your total production volume for the year.
   a. Add together the volume domestically manufactured and the volume imported.
   b. DO NOT subtract the volume used on-site or the volume exported.
3. Divide the volume determined in step 1 by the volume determined in step 2 and multiply by 100.

Additionally, the total percentage of production volume may add up to less than 100 percent if, for example:

- You do not know or cannot reasonably ascertain information about how all of your production volume is processed or used;
- More than 10 combinations of codes are applicable to your chemical substance;
- You export a portion of the production volume;
- A portion of the production volume is used for industrial uses rather than commercial/consumer uses; or

- Percentages round such that they do not sum to 100% (e.g., three use combinations that each account for one-third of total use will be reported as 30% each, totaling 90%).

Table 4-16 provides examples of reporting consumer and commercial use information.

Table 4-16. Examples of Reporting Consumer and Commercial Use Information

Description	Reporting Requirement
Example Site AB manufactures 12,000 lb of Example PFAS AB for processing for incorporation into a mixture. All of the production is for use in commercial products. Of the production volume, 67% (8,000 lb) is used in waterproofing sprays for apparel and 33% (4,000 lb) is used in paper packaging (for non-food use).	On one line, enter CC138 for PC and 70% for production volume. On another line, enter CC301 for PC and 30% for production volume.
Example Site CD manufactures 50,000 lb of Example PFAS CD for processing for incorporation into a mixture. All of the production is for use in commercial products. Of the production volume, 97% (48,500 lb) is used in waterproofing sprays for apparel and 3% (1,500 lb) is used in paper packaging (for non-food use).	On one line, enter CC138 for PC and 100% for production volume. On another line, enter CC301 for PC. Because less than 10% of the production volume is used in paper packaging, enter the percentage to the nearest one percent, i.e., 3%, for production volume.

4.7.2.7 Site-limited?

Indicate whether the PFAS was site-limited. Site-limited means a chemical substance is manufactured and processed only within a site and is not distributed as a chemical substance or as part of a mixture or article outside the site. Imported chemical substances are never site-limited. Report yes if the PFAS was site-limited, no if the PFAS was not site-limited, or NKRA if you do not know and cannot reasonably ascertain whether the PFAS was site-limited.

4.7.2.8 Recycled Volume

Report the volume of the manufactured PFAS, which otherwise would be disposed of as a waste, that is being removed from the waste stream (on site) and is being used for a commercial purpose (40 CFR 705.15(d)(7)). Report the quantity, in pounds, to at least two significant figures; it should be accurate to the extent known to or reasonably ascertainable by you. You should use the same numeric format as described for the domestically manufactured production volume.

Table 4-17 provides examples of reporting recycling activities.

Table 4-17. Examples of Reporting Recycling

Description	Reporting Requirement
Example Site EF manufactures 2,721 lb of Example PFAS EF, none of which is recycled instead of being disposed of as a waste.	Enter 0 as no portion of the chemical is being recycled.
Example Site GH manufactures 5,550 lb of Example PFAS GH, 1,650 lb of which is then recycled instead of being disposed of as a waste.	Enter 1,650 lb as the volume recycled.
Example Site IJ manufactures 52,000 lb of Example PFAS IJ, 10% (1,500 lb) of which is manufactured as a byproduct. That 1,500 lb is then directly recycled and the other 50,500 lb is sold into commerce.	Enter 1,500 lb as the volume recycled.
Example Site KL manufactures a chemical substance, WonderChem. The process to manufacture WonderChem results in the production of a byproduct, Example PFAS KL. Some portion of PFAS KL stays with WonderChem. The remaining portion of PFAS KL is 58,000 lb. Initially Site KL disposed of PFAS KL as a waste, but partway through the year discovered a use for PFAS KL and diverted the remaining portion (29,000 lb) from the waste stream. The full volume of WonderChem is intended for commercial use.	Enter the portion of Example PFAS KL that is being recycled instead of being disposed of as a waste. Do not include any quantity of PFAS KL that stays with and is distributed with WonderChem, because WonderChem is produced for commercial use and no quantity is intended to be disposed of as a waste or recycled. In this case, 29,000 pounds were recycled.
Example Site MN manufactures 12,000 lb of Example Chemical MN for processing by incorporation into a mixture. Of the production volume, 92% (11,040 lb) is processed for incorporation and 8% (960 lb) is shipped to a waste management facility that also recycles certain materials. The manufacturer cannot reasonably ascertain whether this portion of Example PFAS MN is being recycled or disposed of as a waste.	Enter NKRA as the manufacturer does not know and cannot reasonably ascertain whether PFAS MN is being recycled or disposed of as a waste.
Example Site OP manufactures 100% of Example PFAS OP (15,000 lb) as a byproduct. That 15,000 lb is then sold directly to a recycler.	Enter 15,000 lb as the entire volume of Example PFAS OP is known to be recycled rather than disposed of as a waste.

4.8 Part II – Section D. A description of the byproducts resulting from the manufacture, processing, use, or disposal of each such substance or mixture

In this section, report information about all byproducts resulting from the manufacture, processing, use, or disposal of the PFAS. Report information about all byproducts that are chemical substances, regardless of whether the byproducts are themselves PFAS. Information in this section is to be reported for each byproduct for each year. Report all information known to or reasonably ascertainable by you, including byproducts produced during processing, use, or disposal of the PFAS at sites not under your control.

Note that in the case that you produce a PFAS as a byproduct, you may also be required to report that PFAS on its own section 8(a)(7) form. For example, if you are reporting for PFAS A, and PFAS B is produced as a byproduct of manufacturing PFAS A, note that you may also need to complete a section 8(a)(7) form for PFAS B. In that case, you may indicate duplicative reporting for PFAS B in this section.

For purposes of section 8(a)(7) reporting, refer to the following definition of byproduct:

> ***Byproduct*** *means a chemical substance produced without separate commercial intent during the manufacture, processing, use, or disposal of another chemical substance(s) or mixture(s). (40 CFR 704.3)*

> ***Manufacture for commercial purposes*** means:
>
> *(1)* To manufacture, produce, or import with the purpose of obtaining an immediate or eventual commercial advantage, and includes, among other things, the "manufacture" of any amount of a chemical substance or mixture
>
> *(i)* for commercial distribution, including for test marketing, or
>
> *(ii)* for use by the manufacturer, including use for product research and development or as an intermediate.
>
> *(2)* The term also applies to substances that are produced coincidentally during the manufacture, processing, use, or disposal of another substance or mixture, including byproducts that are separated from that other substance or mixture and impurities that remain in that substance or mixture. Byproducts and impurities without separate commercial value are nonetheless produced for the purpose of obtaining a commercial advantage, since they are part of the manufacture of a chemical substance for commercial purposes.

4.8.1 Confidentiality of Byproduct Information

Except for the byproduct source, any information reported in the byproducts section of the section 8(a)(7) form can be claimed as confidential. For all of the data elements in this section, upfront substantiation of the claim is required.

Check the appropriate CBI box in this block and complete the substantiation questions to assert a confidentiality claim for the associated information being submitted. Checking the CBI box automatically triggers the substantiation questions to appear later in the CBI Substantiation portion of the form. See Table 4-5 for substantiation questions related to the byproduct chemical identity and Table 4-13 for substantiation questions related to the other byproduct data elements. **If you do not check the CBI box for any information element, then that information is not claimed as CBI and may be made public without further notice to you**. Further, if you fail to substantiate your CBI claims in accordance with the statute and applicable rules, EPA may make the information available to the public without further notice to you. For

additional information about how to answer substantiation questions, visit *www.epa.gov/tsca-cbi* on the EPA website.

4.8.2 Byproduct Name or Description

Report your chemical substance using the CA Index Name currently used to list the chemical substance on the TSCA Inventory. You can identify the CA Index name by searching SRS using a CASRN, the specific name of the chemical substance, or related acronyms. In the event that an acronym is used for multiple chemical substances, you should take care to select the correct substance. Using the search widget to select a substance will automatically populate both the chemical name and chemical ID.

If the name of the byproduct is unknown, describe the byproduct. The description may be a descriptive name, or you may describe the byproduct as specifically as possible. The description you provide should accurately and precisely convey as much information about the molecular structure of the byproduct as is known to you.

4.8.3 Byproduct Generic Chemical Name [if byproduct chemical name is CBI]

In cases where a chemical substance is listed on the confidential portion of the TSCA Inventory, the generic chemical name will automatically be incorporated into your report when you select the Accession Number.

4.8.4 Byproduct Chemical ID

Report the correct CASRN for your chemical substance if it is listed on the non- confidential portion of the TSCA Inventory. If your chemical substance is listed on the confidential portion of the TSCA Inventory, report the EPA-designated TSCA Accession Number.

If your chemical substance is not on the TSCA Inventory, report the CASRN if one has been assigned. Report "NKRA" only if no CASRN has been assigned to the chemical substance or if the identity of the byproduct is not known to or reasonably ascertainable by you.

Every byproduct reported in accordance with section 8(a)(7) requirements must be accompanied by its correct CASRN, corresponding to the chemical substance's specific chemical name as described in Section4.5.6. (40 CFR 705.15(e)(1)). You may use the search widget to enter either a CASRN or the specific name of the chemical substance to select the appropriate CASRN/Chemical Abstracts (CA) Index Name combination from the SRS database. Using the search widget to select a substance will automatically populate both the chemical name and chemical ID.

In the case of a chemical substance listed on the confidential portion of the TSCA Inventory, report the TSCA Accession Number as the chemical identifying number. Similarly, if a chemical substance has an LVE Number and a CBI claim, the reporter should report the LVE Number as the identifying number.

If the chemical substance is not listed on the TSCA Inventory, report the CASRN if one has been assigned to the chemical substance; report NKRA only if no CASRN, Accession Number, or LVE Number has been assigned or if you do not know and cannot reasonably

ascertain the identity of the byproduct. If you do not know and cannot reasonably ascertain the identity of the byproduct, you must provide a generic, structural description of the byproduct.

4.8.5 Byproduct Source

Indicate whether the byproduct was created as a result of manufacturing, processing, use, and/or disposal. For example, a byproduct created unintentionally while manufacturing a PFAS was created as a result of manufacturing. A byproduct created during management of the PFAS waste, such as a combustion byproduct formed during thermal treatment, is considered to be created as a result of disposal.

4.8.6 Byproduct Release

Indicate whether the byproduct(s) were released to the environment. Select yes, no, or NKRA. For purposes of reporting under this section, "released to the environment" includes quantities of the chemical disposed of in contained land disposal units such as underground injection wells and landfills as well as releases directly to air, water, and soil.

4.8.7 Byproduct Release Medium

If the byproduct(s) were released to the environment, select all media to which the byproducts(s) were released: air, water, or land. If unknown, select NKRA. If the byproduct was not released, report "not applicable."

4.8.8 Byproduct Release Volume

Report the total weight of the byproduct released to all media, in pounds. Report the quantity to at least two significant figures; it should be accurate to the extent known to or reasonably ascertainable by you. Release volumes should be reported in numeric format, without commas (e.g., 6352000). Report only the weight of the byproduct(s) released. Do not include the weight of other materials (e.g., water, solvents, containers, or other chemical substances).

If the byproduct was not released, report "not applicable."

Table 4-18 provides some examples of facilities reporting byproduct information.

Table 4-18. Examples of Byproducts Reporting

Example	Reporting
Example Company QR manufactures Example PFAS QR and is completing the section 8(a)(7) form for Example PFAS QR. During treatment of PFAS QR-containing waste, the site produces 5.0 pounds of hydrogen fluoride. 80% of the hydrogen fluoride is captured by a dry scrubber and spent scrubber medium is disposed of on site in a landfill. The remaining 20% is directly released to air through the site's stacks.	Example Company QR enters CAS # 7664-39-3 as a byproduct. The section 8(a)(7) software populates the CAS name for the chemical, hydrofluoric acid. Company QR reports that the source of this byproduct was disposal. The company reports that the byproduct was released to air and land and 5.0 pounds were released.
Example Site ST manufactures Example PFAS ST and is completing a section 8(a)(7) form for Example PFAS ST. During manufacture of Example PFAS ST, another chemical substance is formed that is also a PFAS, Example PFAS UV. Most of PFAS UV remains in the company's product, but 12 pounds of PFAS UV are released to air on site.	Example Site ST enters the CAS number and CA name of Example PFAS UV and reports manufacturing as its source. Example Site ST reports that PFAS UV was released to air and that releases totaled 12 pounds. Example Site ST also completes a full section 8(a)(7) submission for Example PFAS UV, including reporting these releases in Section G of that reporting form.
Example Site WX manufactures Example PFAS WX. The company knows that during on-site processing of Example PFAS WX, a byproduct is formed, but the company does not know the identity of the byproduct. All of the byproduct produced remains in the company's product and is distributed into commerce.	Example Site WX reviews the information they know and can reasonably ascertain and determines that the specific chemical identity is unknown. Example Site WX provides a description of the byproduct and indicates "NKRA" for the Chemical ID. Example Site WX indicates that the byproduct was produced during processing and that the byproduct was not released to the environment. The site reports "N/A" for the byproduct release medium and release volume.
Example Site YZ manufactures Example PFAS YZ. During manufacture of Example PFAS YZ, two byproducts are formed, Example PFAS AA and Example PFAS BB. PFAS AA is separated from the mixture and all 150 pounds produced are disposed of in the site's on-site landfill. Most of PFAS BB remains in the product and is distributed into commerce. The company knows some amount of PFAS BB is released to air on site but cannot determine how much.	Example Site YZ first reports the chemical name and CAS number for PFAS AA and indicates that PFAS AA is produced during manufacturing. Site YZ reports that 150 lb of PFAS AA are disposed of to land. Next, Site YZ enters the name and CAS number of PFAS BB as another byproduct. For PFAS BB, the company reports its source as manufacturing and reports that it is released, to air, with total release quantity NKRA.

4.9 Part II – Section E. All existing information concerning the environmental and health effects of such substance or mixture

In this section, report all information concerning the environmental and health effects of the substance or mixture that is known to or reasonably ascertainable by you. This information includes but is not limited to:

- Toxicity information (e.g., in silico, in vitro, animal test results, human data); and
- Other data relevant to environmental and health effects including range-finding studies, preliminary studies, OSHA medical screening or surveillance standards reports, adverse effects reports.

4.9.1 Confidentiality of Environmental and Health Effects Information

Information reported in this section of the PFAS data reporting form can be claimed as confidential, but reporters should note that TSCA section 14(b) places significant limitations on confidentiality protections for information from health and safety studies. CBI claims for environmental and health effects are only valid if they would disclose certain information related to a company's process or operations used in the manufacturing of the chemical. For all of the data elements in this section, upfront substantiation of the claim is required. For any environmental or health effects information being claimed as CBI, you must also submit a sanitized version (omitting only information that is claimed as confidential and appropriately substantiated) of the study report or other attachment for public release.

Check the appropriate CBI box in this block and complete the substantiation questions to assert a confidentiality claim for the associated information being submitted. Checking the CBI box automatically triggers the substantiation questions to appear later in the CBI Substantiation portion of the form. See Table 4-5 for substantiation questions related to the byproduct chemical identity and Table 4-13 for substantiation questions related to other data elements. Further, **if you fail to substantiate your CBI claims *and to provide a sanitized version of the report or attachment* in accordance with the statute and applicable rules, EPA may make the information available to the public without further notice to you**. For additional information about how to answer substantiation questions, visit *www.epa.gov/tsca-cbi* on the EPA website. Redactions must be as sparing as possible. It is your responsibility to ensure that any sanitized reports are thoroughly sanitized. EPA may publicly release sanitized reports as provided by you. It is your responsibility to ensure you have fully sanitized the report and that any changes or redactions cannot be reversed in the submitted sanitized version.

4.9.2 OECD Harmonized Environmental and Health Effects Template (attachment)

Upload all known or reasonably ascertainable information concerning the environmental and health effects of the substance or mixture, using OECD Harmonized Templates (OHTs) if available for the endpoint being reported on. OHTs are available from the OECD website: *https://www.oecd.org/ehs/templates/harmonised-templates.htm*. This can be accomplished by using the freely available IUCLID6 software (*https://iuclid6.echa.europa.eu/*), exporting the dossier in the OHT working context, and uploading via this rule's reporting tool. As of this writing, EPA uses IUCLID6 v6.27.2; submitters using future IUCLID6 v7 can export their dossier via the "Export to previous major version" function described in the IUCLID Manual (*https://iuclid6.echa.europa.eu/documents/1387205/1809908/iuclid_functionalities_html_en.pdf/9d01cb53-902d-dbb6-fb00-fa141688c395?t=1667168830907*). Submitters using future versions IUCLID6 v8 and higher (such as IUCLID7) should consult with EPA before submitting

their data to confirm the current data format acceptance standards. EPA can accept any dossiers generated using an earlier version of IUCLID6. You may already have data in this format if the company has submitted the studies under the European Union's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation.

The reporting software will guide you through the process of uploading attachment(s).

4.9.3 Study Report (attachment)

Upload as attachment(s) any relevant study report(s). You are required to provide any test data on the health and environmental effects of the PFAS in your possession or control, and a description of any other health and environmental effects data on the substance known to or reasonably ascertainable by you. Data in the possession or control of either a parent company or an affiliated subsidiary located outside the U.S. are considered by the Agency to be data that should be known to or reasonably ascertainable by a submitter.

Data must be submitted in English. Standard literature citations may be submitted for data in the open scientific literature. Complete test data (not summaries) must be submitted if they do not appear in the open literature. Incomplete reports (e.g., from ongoing studies) are exempt from full reporting. However, you must describe the nature and objective of any incomplete study, report, or test, the name and address of any laboratory developing the data; progress to date; type of data collected; significant preliminary results; and an anticipated completion date. If significant preliminary results or final results are obtained prior to the submission deadline or any other additional information significant to the review of the notice becomes available to you, you must submit this information. This includes reports from studies not conducted by your company, such as studies commissioned by your company. The reporting software will guide you through the process of uploading attachment(s). You may consider developing and voluntarily submitting a robust study summary along with the record as EPA is interested in the potential utility of this information to reduce the future burden of reporting, but this may not be submitted in lieu of a full study report.

4.9.4 Supporting Information (attachment)

Upload as attachments any relevant supporting information. This section is intended for you to provide any supporting information related to the study reports uploaded in the previous section. Other data not related to the uploaded study reports will be uploaded in the "Other Data Relevant to Environmental or Health Effects" section (i.e., section 4.9.6 below). The reporting software will guide you through the process of uploading attachment(s).

4.9.5 Analytical/Test Methods

Use the text entry field to describe any and all known analytical or test methods for the PFAS substance. If the method is an EPA method or is substantially similar to an EPA method, you may state which EPA method is the basis of the test method used and clearly describe all modifications. If the method is not an EPA method or substantially similar to an EPA method, describe all steps of the method in as much detail as possible. Standard literature citations may

be submitted for test methods described in the open scientific literature. Complete method descriptions (not summaries) must be submitted if they do not appear in the open literature.

4.9.6 Other Data Relevant to Environmental or Health Effects

Provide, as attachments, any other data relevant to environmental or health effects not published in a study report. Such information may include, but is not limited to, material safety data sheets (SDS), information on physical/chemical properties, preliminary studies, range-finding studies, OSHA medical screening or surveillance standards reports, adverse effects reports, anonymized or aggregated informal test results in workers, underlying environmental monitoring data, blood levels, or inhalation studies.

4.10 Part II – Section F. The number of individuals exposed, and reasonable estimates of the number who will be exposed, to such substance or mixture in their places of employment and the duration of such exposure

In this section, report information concerning workers' exposure to the PFAS. Reporting in this section includes information on the activities resulting in exposure, number of workers exposed and the maximum duration of exposure, at the manufacturing site as well as industrial users and commercial sites.

Information in this section may depend on knowledge of activities occurring at sites not under your control. Recall that information provided under section 8(a)(7) reporting follows the "known to or reasonably ascertainable" reporting standard, which may entail requesting information from downstream users. Refer to Section 4.2 of this Guidance Document for a discussion of the reporting standard.

4.10.1 Confidentiality of Worker Exposure Information

Information reported in the worker exposure section of section 8(a)(7) reporting can be claimed as confidential. For all of the data elements in this section, upfront substantiation of the claim is required.

Check the appropriate CBI box in this block and complete the substantiation questions to assert a confidentiality claim for the associated information being submitted. Checking the CBI box automatically triggers the substantiation questions to appear later in the CBI Substantiation portion of the form. See Table 4-13 for substantiation questions related to these data elements. **If you do not check the CBI box for any information element, then that information is not claimed as CBI and may be made public without further notice to you.** Further, if you fail to substantiate your CBI claims in accordance with the statute and applicable rules, EPA may make the information available to the public without further notice to you. For additional information about how to answer substantiation questions, visit *www.epa.gov/tsca-cbi* on the EPA website.

4.10.2 Worker Activity Descriptions

Describe the activities for workers at the manufacturing site. For example:

- Workers unload totes of the PFAS from delivery trucks into different containers in site chemical storage area.
- Workers take samples of the product for QA/QC testing.
- Workers clean reaction vessels which contain residual PFAS product and reactants.

4.10.3 Number of Workers Exposed at the Manufacturing Site

For each activity listed above, report the total number of workers reasonably likely to be exposed to the reportable PFAS at the manufacturing site (40 CFR 711.15(g)). Select the code corresponding to the appropriate range for the number of workers reasonably likely to be exposed to the PFAS during manufacture. Table 4-19 lists the codes and ranges.

Table 4-19. Codes for Reporting Number of Workers Reasonably Likely to be Exposed

Code	Range of Workers Reasonably Likely to be Exposed
W1	Fewer than 10 workers
W2	At least 10 but fewer than 25 workers
W3	At least 25 but fewer than 50 workers
W4	At least 50 but fewer than 100 workers
W5	At least 100 but fewer than 500 workers
W6	At least 500 but fewer than 1,000 workers
W7	At least 1,000 but fewer than 10,000 workers
W8	At least 10,000 workers

"Reasonably likely to be exposed" means "an exposure to a chemical substance which, under foreseeable conditions of manufacture, processing, distribution in commerce, or use of the chemical substance, is more likely to occur than not to occur. Such exposures would normally include, but would not be limited to, activities such as charging reactor vessels, drumming, bulk loading, cleaning equipment, maintenance operations, materials handling and transfers, and analytical operations. Covered exposures include exposures through any route of entry (inhalation, ingestion, skin contact, absorption, etc.), but excludes accidental or theoretical exposures" (40 CFR 711.3).

Persons reasonably likely to be exposed to a chemical substance include workers whose employment requires them to pass through areas where chemical substances are manufactured, processed, or used (e.g., production workers and foremen, process engineers, and plant managers). Workers employed to drive vehicles which transport the chemical

substance should be included in the number of workers reasonably likely to be exposed to the chemical substance if they come into contact with the chemical substance during loading or unloading. For example, workers engaged in the connection or disengagement of hoses used to load or unload the chemical substance should be included. However, workers involved solely with transporting chemical substances in sealed containers that are totally enclosed with no potential for exposure should not be included.

In addition, when a site employs temporary, seasonal, or contract workers in the manufacture of a reportable chemical substance, these workers should be included in the number of workers reasonably likely to be exposed to a chemical substance if they work in areas where the chemical substance is manufactured. The term does not include those employees whose jobs are not associated with potential exposures to a chemical substance or mixture (e.g., administrative staff who never enter areas where the chemical substance is manufactured) and who are unlikely to be exposed to a chemical substance for even a brief period of time.

No allowance is made for personal protective equipment or for engineering controls that reduce but do not preclude exposure to a chemical substance; however, if contact between a worker and a chemical substance is highly improbable, the worker should not be included among those persons reasonably likely to be exposed to the chemical substance.

Workers are considered to be exposed even if the chemical does not enter the body. For instance, skin contact with a PFAS-containing article is considered an exposure if the worker comes into contact with the PFAS, even if it is believed not to migrate from the article or is not dermally absorbed.

There is no minimum duration or frequency of exposure for determining the number of workers reasonably likely to be exposed to a chemical substance. If it is determined that a worker is reasonably likely to be exposed at any time during the year for any length of time, this worker should be included in the estimate.

There is no minimum level of exposure to a PFAS below which a worker need not be counted among the number reasonably likely to be exposed to a chemical substance. Therefore, if a company knows that a chemical substance manufactured at the site is present in the air throughout the site, all workers at the site must be included in the number of workers reasonably likely to be exposed to the chemical substance.

When there is no potential exposure to a chemical substance, the code W1 corresponding to fewer than 10 workers would be reported. This would be the case, for instance, when a chemical substance is imported in sealed containers and resold without repackaging or is shipped from a foreign source directly to a customer.

Throughout this section, for clarity, the terms “exposed” and “exposure” are used to mean “reasonably likely to be exposed” and “reasonably likely exposure.”

4.10.4 Maximum Duration of Exposure for Manufacturing Workers

For each activity reported, indicate the maximum duration of exposure for any worker at the manufacturing site in hours per day and the maximum number of days per year that workers may be exposed. If workers have different lengths of exposure (for example, due to shift schedules or different job roles), consider two scenarios: the worker(s) who have the longest duration of exposure on any day of the year (called maximum daily exposure), and the worker(s) who are exposed on the highest number of days per year (called maximum annual exposure). For each of these workers, report the maximum duration of exposure on any single day as well as the number of days per year that the worker is reasonably likely to be exposed. For each activity, consider the following questions:

1) What worker or group of workers is exposed for the longest amount of time on any one day doing this activity?
    a. How long is that maximum amount of time that the worker or group of workers is exposed doing this activity?
    b. On how many days per year is this worker(s) exposed to the PFAS while doing this activity?
2) What worker or group of workers is exposed on the largest number of days each year doing this activity?
    c. How many days per year is that worker or group of workers exposed doing this activity?
    d. What is the longest amount of time that worker(s) is exposed doing this activity on any one day?

Report maximum daily exposure to the nearest hour, except for workers exposed for less than one hour. Report 1 hour for any worker exposed for less than one hour; do not round to zero. If you know the duration of exposure to a greater degree of precision than the nearest hour, report the more precise information. If work shifts at your site cross midnight, you may consider the work shift to be one day (e.g., a worker who is exposed on one shift from 10 PM until 6 AM the next day may be counted as one day of exposure and 8 hours of daily exposure). Recall that in this section, you are reporting exposure by activity. If a worker at your site may be exposed to the PFAS during multiple activities, report for each activity considering that activity alone, and not any other activities.

Table 4-20 shows how companies would report in various example scenarios.

Table 4-20. Example manufacturing worker exposure scenarios

Exposure Scenario	Exposure for worker(s) with maximum daily exposure	Exposure for worker(s) with maximum annual exposure
Example Site CC has reported reaction vessel clean-outs as an activity with worker exposure to Example PFAS CC. Production line workers perform one thorough clean out per year, which takes 10 hours, and less-thorough monthly clean-outs, which each take 5 hours, for a total of 12 cleanings per year. The same workers perform all cleanouts.	Report 10 hours as the maximum daily exposure, because this is the longest duration of exposure for workers on any single day. Report 12 days as the maximum annual frequency, because these workers are exposed up to 12 days per year.	In this case, this activity is only done by one group of workers, so the workers with the maximum daily exposure are also the workers with the maximum annual exposure. Report 10 hours as the maximum daily exposure and 12 days as the maximum annual frequency.
At Example Site DD, workers may be exposed to Example PFAS DD when charging reactor vessels, a process that usually takes one hour but sometimes takes up to two hours. Reactor vessels are charged every day and the site operates 360 days per year, but no one worker works more than 5 days per week, or 260 days per year.	Report 2 hours as the maximum daily exposure, because this is the longest amount of time the activity takes. Report 260 days per year as the maximum annual exposure, because any single exposed worker may be exposed up to 260 days per year.	In this case, this activity is only done by one group of workers, so the workers with the maximum daily exposure are also the workers with the maximum annual exposure. Report 2 hours as the maximum daily exposure and 260 days as the maximum annual frequency.
Example Site EE imports Example PFAS EE in sealed vessels, re-labels the containers, and ships the containers without repackaging. No workers are expected to be exposed to PFAS EE.	Because no activities resulting in worker exposure occurred, report "N/A" for this section.	Because no activities resulting in worker exposure occurred, report "N/A" for this section.
Workers at Example Site FF are reasonably expected to be exposed to Example PFAS FF while charging reactor vessels, which takes no more than 3 hours. Reactor vessels are charged every day. The site rotates staff duties, so that no worker performs reactor vessel charging more than one day per week, or 52 times per year. Line supervisors may also be briefly exposed to PFAS FF during this activity. Supervisory duties are split equally between two workers, so that each performs this duty 180 days per year.	The workers with the maximum daily exposure for this activity are the workers actually charging reaction vessels, who may be exposed for up to 3 hours in a single day. Report 3 hours for the maximum daily exposure in this section. These workers are exposed up to 52 days per year, so report 52 days as the maximum annual exposure in this section.	The workers with the maximum annual exposure for this activity are the supervisors, who may each be exposed for up to 180 days during the year. These workers are exposed for no more than 15 minutes on any given day. Report 1 hour (do not round exposures less than one half-hour down to zero) for the maximum daily exposure and 180 days as the maximum annual exposure in this section.

Exposure Scenario	Exposure for worker(s) with maximum daily exposure	Exposure for worker(s) with maximum annual exposure
Workers at Example Site GG are exposed to Example PFAS GG during two activities: transferring the chemical from totes to smaller vessels and cleaning empty totes. Workers transfer the chemical from totes multiple times per day, resulting in total daily exposure of up to one hour. Workers perform this activity at the site up to 208 days per year. Empty totes are cleaned twice a year and the process takes two hours. The same workers do both tasks.	Transfer to smaller vessels: Workers are exposed to PFAS GG for a maximum of 1 hour per day while transferring the chemical. This exposure may happen on a maximum of 208 days per year. Report 1 hour per day and 208 days per year for this activity. Tote cleaning: Workers are exposed to PFAS GG for up to two hours while cleaning totes, which may occur a maximum of two days per year. Report 2 hours and 2 days per year for this activity.	In this case, the workers with the maximum daily exposure and maximum annual exposure are the same for each activity. Report 1 hour per day and 208 days per year for chemical transfer and 2 hours and 2 days per year for tote cleaning. Note that although the same workers perform both activities, reporting in this section is by activity. Do not combine exposure from multiple activities when reporting in this section.

4.10.5 Number of Workers Exposed for each Industrial Process and Use

For each unique combination of Type of Process or Use Operation, Industrial Sector, and Function Category, estimate the total number of workers that are reasonably likely to be exposed to the chemical substance at sites that process or use the chemical substance (40 CFR 711.15(g)(4)). Include workers at sites that are not under your control as well as those sites you control. For each combination of TPU, sector, and function, report the code that corresponds to the estimated range of the number of workers reasonably likely to be exposed. Table 4-19 shows the codes and worker ranges. See Section 4.10.3 for a discussion of "reasonably likely to be exposed."

4.10.6 Maximum Duration of Exposure for Industrial Workers

For each unique combination of Type of Process or Use Operation, Industrial Sector, and Function Category, estimate the maximum duration of exposure for workers that are reasonably likely to be exposed to the chemical substance at sites that process or use the chemical substance. Include workers at sites that are not under your control as well as those sites you control.

If workers have different lengths of exposure (for example, due to shift schedules or different job roles), consider two scenarios: the worker(s) who have the longest duration of exposure on any day of the year (called maximum daily exposure), and the worker(s) who are exposed on the highest number of days per year (called maximum annual exposure). For each of these workers, report the maximum duration of exposure on any single day as well as the number of days per year that the worker is reasonably likely to be exposed. For each activity, consider the following questions:

1. What worker or group of workers is exposed for the longest amount of time on any one day for this combination of Type of Process or Use Operation, Industrial Sector, and Function Category?
    a. How long is that maximum amount of time that the worker or group of workers is exposed for this TPU/IS/FC combination?
    b. On how many days per year is this worker(s) exposed to the PFAS for this TPU/IS/FC combination?

2. What worker or group of workers is exposed on the largest number of days each year doing this activity?
    a. How many days per year is that worker or group of workers exposed for this TPU/IS/FC combination?
    b. What is the longest amount of time that worker(s) is exposed for this TPU/IS/FC combination?

Report maximum daily exposure to the nearest hour, except for workers exposed for less than one hour. Report one hour for any worker exposed for less than one hour; do not round to zero. If work shifts cross midnight, you may consider the work shift to be one day (e.g., a worker who is exposed on one shift from 10 PM until 6 AM the next day may be counted as one day of exposure and 8 hours of daily exposure). Recall that in this section, you are reporting exposure by activity. If a worker at your site may be exposed to the PFAS during multiple activities, report for each activity considering that activity alone, and not any other activities.

Table 4-21. Example industrial worker exposure scenarios

Exposure Scenario	Exposure for worker(s) with maximum daily exposure	Exposure for worker(s) with maximum annual exposure
Example Site HH incorporates Example PFAS HH into a metalworking fluid. Site HH knows that workers at its customers' facilities may work with the metalworking fluid for an entire shift and are reasonably likely to be exposed to the PFAS during this activity, which may occur on a daily basis. Site HH also knows its customers operate on 4x10-hour shift schedule, and therefore exposed workers are likely to be exposed for up to 10 hours per day, up to 4 days per week, or 208 days per year.	Report 10 hours per day as the maximum duration per day for this this combination of Type of Process or Use Operation, Industrial Sector, and Function Category. Report 208 days per year as the maximum duration per year.	In this case, this activity is only done by one group of workers, so the workers with the maximum daily exposure are also the workers with the maximum annual exposure. Report 10 hours as the maximum daily exposure and 208 days as the maximum annual frequency.

Exposure Scenario	Exposure for worker(s) with maximum daily exposure	Exposure for worker(s) with maximum annual exposure
Example Site II manufactures Example PFAS II and processes the chemical on site. The site knows that its processing activity is reasonably expected to expose workers for no more than 3 hours per day and occurs on Monday and Thursday every week. One group of production workers performs the activity on Mondays and a different group of workers performs the activity on Thursdays. One supervisor may also be exposed for no more than one hour during the activity. The same supervisor oversees the activity every time it is performed.	The workers with the most exposure on any given day are the production workers, who are exposed for up to 3 hours per day. Report 3 hours per day for the workers with the maximum daily exposure for this combination of TPU, IS, and FC codes. Report 52 days as the maximum duration per year for workers with the maximum daily exposure for this this combination of TPU, IS, and FC codes, because no single production worker is exposed more than one day per week, or 52 days per year.	The worker with the largest number of days of exposure is the supervisor, who may be exposed twice per week, or 104 days per year. The supervisor is not exposed for more than one hour per day during this activity, so report 1 hour for the maximum daily exposure for the worker with maximum annual exposure. Report 104 days per year for the maximum annual frequency of exposure for the worker with the maximum daily exposure.
Example Site JJ imports a PFAS chemical in an article. The PFAS chemical is part of a non-stick coating on the inside of equipment and workers are not expected to have physical contact with the internal non- stick surface.	Report N/A for this combination of TPU, IS, and FC codes.	Report N/A for this combination of TPU, IS, and FC codes.

4.10.7 Number of Workers Exposed for each Commercial Use

Report the total number of commercial workers, including those at sites not under your control that are reasonably likely to be exposed while using the reportable chemical substance, with respect to each commercial use (40 CFR 705.15(g)(5)). For each combination of commercial Product Category and Function Category reported (Section4.6), report the code which corresponds to the appropriate range of commercial workers reasonably likely to be exposed. Table 4-19 shows the codes for numbers of workers. See Section 4.10.3 for a discussion of “reasonably likely to be exposed.”

4.10.8 Maximum Duration of Exposure for Commercial Workers

For each unique combination of Product Category and Function Category, estimate the maximum duration of exposure for workers that are reasonably likely to be exposed to the chemical substance at sites that process or use the chemical substance. Include workers at sites that are not under your control as well as those sites you control.

If workers have different lengths of exposure (for example, due to shift schedules or different job roles), consider two scenarios: the worker(s) who have the longest duration of exposure on any day of the year (called maximum daily exposure), and the worker(s) who are exposed on the highest number of days per year (called maximum annual exposure). For each of these workers, report the maximum duration of exposure on any single day as well as the

number of days per year that the worker is reasonably likely to be exposed. For each activity, consider the following questions:

1. What worker or group of workers is exposed for the longest amount of time on any one day for this combination of Product Category and Function Category?
    a. How long is that maximum amount of time that the worker or group of workers is exposed for this PC/FC combination?
    b. On how many days per year is this worker(s) exposed to the PFAS for this PC/FC combination?
2. What worker or group of workers is exposed on the largest number of days each year doing this activity?
    a. How many days per year is that worker or group of workers exposed for this PC/FC combination?
    b. What is the longest amount of time that worker(s) is exposed for this PC/FC combination?

Report maximum daily exposure to the nearest hour, except for workers exposed for less than one hour. Report one hour for any worker exposed for less than one hour; do not round to zero. If work shifts cross midnight, you may consider the work shift to be one day (e.g., a worker who is exposed on one shift from 10 PM until 6 AM the next day may be counted as one day of exposure and 8 hours of daily exposure). Recall that in this section, you are reporting exposure by activity. If a worker may be exposed to the PFAS during multiple activities, report for each activity considering that activity alone, and not any other activities.

Table 4-22. Example commercial worker exposure scenarios

Exposure Scenario	Exposure for worker(s) with maximum daily exposure	Exposure for worker(s) with maximum annual exposure
Example Company KK incorporates Example PFAS KK into a lubricating wax. Many of its customers are sporting good rental and repair shops, including ski shops and bike shops. Company KK knows that workers are likely exposed to the PFAS when applying lubricating waxes to equipment, an activity that may be done intermittently throughout a shift. Company KK knows from discussions with its customers that ski shops use the wax daily during the ski season, and that workers work up to 12 hour shifts up to 5 days per week during this 20-week season; the shops are closed the rest of the year. Bike shops using these products operate with shifts no longer than 10 hours long, up to 5 days per week year round.	The ski shop workers in this scenario have the longest maximum exposure on any given day and should be considered the workers with the maximum daily exposure. The ski shop workers work up to 12 hours at a time. Although exposure is intermittent, these workers may be exposed throughout the 12 hour shift. Company KK reports 12 hours as the maximum daily exposure. The ski shop workers work up to 100 days per year, so Company KK reports 100 days per year as the maximum annual exposure for the workers with the maximum daily exposure.	The bike shop workers in this scenario are exposed for the most days per year and should be considered the workers with the maximum annual exposure. Bike shop workers work up to 10 hours at a time. Although exposure is intermittent, these workers may be exposed throughout the 10 hour shift. Company KK reports 10 hours as the maximum daily exposure for the workers with maximum annual exposure. The bike shop workers work up to 260 days per year, so Company KK reports 260 days per year as the maximum annual exposure.
Example Company LL uses PFAS LL as a stain-resistant coating for carpets sold to commercial customers. Company LL knows from news reports that PFAS from coated carpets can be released into indoor air and dust over time, resulting in worker exposure. Company LL assumes that its commercial customers operate with 8 hours shifts and that workers work five days per week, 52 weeks per year.	Example Company LL estimates that workers in commercial customers using its carpets are exposed for eight hours per day, five days per week. Example Company LL reports 8 hours as the maximum daily exposure and 260 days as the maximum annual exposure for workers with the maximum daily exposure.	In this case, this Product Category/Function Category for Example PFAS LL is only done by one group of workers, so the workers with the maximum daily exposure are also the workers with the maximum annual exposure. Company LL reports 8 hours as the maximum daily exposure and 260 days as the maximum annual exposure for workers with the maximum annual exposure.
Example Site MM produces a PFAS-coated part used in commercial machines. The PFAS is not expected to produce any emissions or migrate from the coating under normal conditions of use.	Site MM reports 0 hours per day and 0 days per year, as workers are not expected to be exposed for any amount of time.	Site MM reports 0 hours per day and 0 days per year, as workers are not expected to be exposed for any amount of time.

4.11 Part II – Section G. The manner or method of its disposal, and in any subsequent report on such substance or mixture, any change in such manner or method

4.11.1 Confidentiality of Disposal Information

Information reported in the disposal section of the section 8(a)(7) reporting form can be claimed as confidential if it is not already public information. For all of the data elements in this section, upfront substantiation of the claim is required.

Check the appropriate CBI box in this block and complete the substantiation questions to assert a confidentiality claim for the associated information being submitted. Checking the CBI box automatically triggers the substantiation questions to appear later in the CBI Substantiation portion of the form. See Table 4-13 for substantiation questions related to these data elements. **If you do not check the CBI box for any information element, then that information is not claimed as CBI and may be made public without further notice to you.** Further, if you fail to substantiate your CBI claims in accordance with the statute and applicable rules, EPA may make the information available to the public without further notice to you. For additional information about how to answer substantiation questions, visit *www.epa.gov/tsca-cbi* on the EPA website.

4.11.2 Manner or Method of Disposal

If the PFAS is disposed of, report the method of disposal using a code or codes from Table 4-23. Report all disposal controlled by the site (e.g., include shipments of waste for disposal to third parties). You are not required to report disposal by downstream users. Provide additional description of the disposal method as needed; additional description is required for code D99 "other." For each year, report any disposal methods(s) used during that year. You will be prompted to and are required to report disposal in any year from 2011 to 2022, even if you did not manufacture the PFAS in each year. For example, if you manufactured a PFAS in 2014, 2015, and 2016, and disposed of remaining waste containing that PFAS in 2017, you must include the disposal that occurred in 2017 even though you did not manufacture the PFAS that year.

If the PFAS is not disposed of in a given year, select "N/A" for that year. If you do not know and cannot reasonably ascertain whether the PFAS is disposed of, or if you know the PFAS is disposed of but do not know and cannot reasonably ascertain the method of disposal, select "NKRA."

Table 4-23. Disposal Process codes

Code	Description
D1	On-site land disposal: RCRA Class C landfill (hazardous)
D2	On-site land disposal: Other landfill

Code	Description
D3	Other on-site land disposal
D4	On-site underground injection (UIC)
D5	Off-site land disposal: RCRA Class C landfill (hazardous)
D6	Off-site land disposal: Other landfill
D7	On-site incineration
D8	Off-site incineration
D9	Publicly owned treatment works (POTW)
D10	Other off-site waste transfer
D11	On-site release to surface water
D12	On-site release to air (stack emissions)
D13	On-site release to air (fugitive emissions)
D99	Other

4.11.3 Changes in Disposal Methods

Use the free text field to describe any changes to the disposal process or methods since January 1, 2011.

4.11.4 Release Quantity

Report the total weight of the PFAS released to each medium (i.e., air, water, or land) in pounds. Report the quantity to at least two significant figures; it should be accurate to the extent known to or reasonably ascertainable by you. Release volumes should be reported in numeric format, without commas (e.g., 6352000). ***Report only the weight of the specific PFAS released***. Do not include the weight of any other materials (e.g., water, solvents, containers, or other chemical substances). Consider all possible sources of releases, including treated waste streams. For example, incineration of PFAS waste may not fully destroy the PFAS and there may be air releases of the PFAS associated with this process.

Table 4-24. Release media for disposal codes

Code	Description	Release Medium
D1	On-site land disposal: RCRA Class C landfill (hazardous)	Land
D2	On-site land disposal: Other landfill	Land
D3	Other on-site land disposal	Land
D4	On-site underground injection (UIC)	Land

Code	Description	Release Medium
D5	Off-site land disposal: RCRA Class C landfill (hazardous)	Land
D6	Off-site land disposal: Other landfill	Land
D7	On-site incineration	If combustion is incomplete, PFAS may remain in stack air emissions, ash, or scrubber blowdown, filter material, etc., and may be released to any medium
D8	Off-site incineration	Report off-site release media to the extent known to or reasonably ascertainable by you.
D9	Publicly owned treatment works (POTW)	Water
D10	Other off-site waste transfer	Report off-site release media to the extent known to or reasonably ascertainable by you.
D11	On-site release to surface water	Water
D12	On-site release to air (stack emissions)	Air
D13	On-site release to air (fugitive emissions)	Air
D99	Other	

4.11.5 Incineration Quantity and Temperature

Report the total weight of the PFAS incinerated on-site each year. If on-site incineration occurred, also report the incineration temperature (in degrees Celsius). If incineration occurred at multiple temperatures, indicate the minimum temperature (in degrees Celsius) at which the PFAS was incinerated. Report only the weight of PFAS destroyed by incineration. Quantities of PFAS not destroyed (e.g., released to air or remaining in ash) should be reported as releases in the previous section.

4.12 Optional Information

This section consists of a text field for submitting additional information. Use this field to provide any additional information about your submission that may be relevant.

4.13 Joint Submissions

4.13.1 Determining the Need for a Joint Submission

Joint submissions are required in those instances where a company (e.g., foreign supplier, contracting company) will not disclose to the manufacturer (including importer)

certain chemical substance identifiers (i.e., CASRN, Accession number, or LVE number), due to confidentiality concerns.

This may happen, for instance, when a company is importing a mixture under a trade name, and the foreign manufacturer refuses to reveal the chemical identity of a confidential component of the mixture. In this case, the importer and the supplier can each separately report their portion of the required information, resulting in a joint submission. The importer must ask the supplier of the confidential chemical substance to directly provide EPA with the correct chemical identity (see 40 CFR 705.15(b)(iii)).

A manufacturer (including importer) can identify, on a chemical-by-chemical basis, the supplier for a chemical substance. The reporting tool will generate a unique ID number for each chemical substance (identified by a trade name). Therefore, a supplier may receive multiple ID numbers from a manufacturer (including importer). A supplier may also report multiple chemical substances under one ID number in the case that the ID number refers to a mixture. In that situation, the supplier will be identifying the PFAS that comprise the mixture.

It is the responsibility of the primary submitter to ask its supplier, or secondary submitter, to send the information to EPA by the end of the submission period. The reporting tool leads the primary submitter through this notification process.

If the secondary submitter decides to provide the required trade name product information directly to you, you should change your submission type and submit a single submission.

Note that not all submitters are required to initiate joint submissions. Article importers using the article importer reporting form will not be required or have the option to initiate joint *submissions.* Additionally, if a secondary submitter is not known or reasonably ascertainable to the PFAS manufacturer (e.g., if a foreign supplier is no longer in business and has no successor entity), then the manufacturer would indicate that the secondary submitter is NKRA and need not initiate a joint submission.

4.13.2 The Primary Submission is Completed by the PFAS Manufacturer

The primary submitter for a joint submission is either an importer or a manufacturer of a PFAS of unknown chemical identity (i.e., CASRN, TSCA Accession number, or LVE number). For ease of presentation, both types of primary submitters will be referred to as “importer.” The importer, as the primary submitter, is responsible for initiating the joint submission. The importer uses the reporting tool to notify the secondary submitter (e.g., its supplier or contract manufacturer) of the need to complete the secondary portion of the joint submission, and completes the sections related to manufacturing (Part II.A – C), processing and use (Part II.D), byproducts (Part II.D), environmental and health effects (Part II.E), (40 CFR 705.15(f)) and the processing and use-related section (Part II.D) (40 CFR 705.15(c)) for the imported substance.

Identifying the chemical identity of the unknown chemical substance and its secondary submitter

In its portion of the joint submission, the primary submitter identifies the proprietary substance or mixture using the trade name or another name, additional information as needed to help the secondary submitter correctly identify the substance, and the identity and contact information for the secondary submitter. See Sections 4.4.2 and 4.5.11 for additional information.

Notifying the secondary submitter about the joint submission

Using the reporting tool, the importer enters the email address of the secondary submitter, and any necessary instruction for the secondary submitter to complete its part of the joint submission, into a system generated email. Also contained within the email is the unique identifier. The importer will need to click the link to send this information from CDX to the Secondary Authorized Official. Additional recipients may be added by the importer. The primary submitter may send the email before it has completed its part of the joint submission.

Completing the primary portion of the joint submission

The importer is responsible for completing the rest of Part II of the form as it relates to the proprietary substance or mixture. See Sections 4.7 through 4.12 of this document for additional information about completing Part II.

4.13.3 The Secondary Submission is Completed

The secondary submitter is responsible for identifying that it is providing information for the joint submission using the information (e.g., identification number) provided by the primary submitter and completing the Secondary Form.

4.13.3.1 Receiving notification from the primary submitter about the joint submission

The secondary submitter receives an email from the primary submitter identifying that a joint submission has been initiated and providing the unique identification number needed for the secondary submitter to complete its part of the joint submission.

4.13.3.2 Completing the Secondary Form, the secondary portion of the joint submission

The secondary submitter is responsible for completing the Secondary Form of the joint submission, which includes its company identity, a technical contact, identification of its customer (i.e., the primary submitter), the product trade name, and the unique identifier supplied by the primary submitter. The secondary submitter then provides the chemical identity and percentage of formulation of each PFAS in the product. See Section 4.54.5 for information about chemical identity.

4.13.3.3 When the Supplier Doesn't Know the Chemical Identity

There may be instances where a foreign supplier (i.e., secondary submitter) purchases a mixture, under a trade name, from another company (tertiary company) and does not know the

chemical components of the mixture. The foreign supplier can ask the company manufacturing the trade secret mixture or chemical substance to directly provide EPA with the correct chemical identity. In this case, the tertiary company would register with CDX and use the Unique Identifier for Joint Submissions, sent to the foreign supplier by the manufacturer (including importer), to complete the form.

Under this scenario, the foreign supplier does not have access to any of the information submitted to EPA by the tertiary company. Likewise, the tertiary company cannot see the information the foreign supplier reports to EPA. This way, the confidentiality of information for both the foreign supplier and tertiary company is protected.

4.13.4 Confidentiality of Information Jointly Submitted

All of the confidentiality requirements discussed earlier in these Instructions apply to information submitted jointly. However, joint submissions include information required to connect the two reports and their related data. For example, a joint submission requires that the primary submitter provide a generic chemical name or trade name and secondary submitter's identity. A secondary submitter would provide the composition of its product.

These data elements specific to joint submissions require that any claims of confidentiality be asserted at the time of submission, but do not require upfront substantiation (pursuant to TSCA section 14(c)(2)):

- Joint submission information from the primary submitter consisting of trade name and supplier identification required pursuant to § 705.15(b)(1)(i) and § 705.18(b)(2)(i).
- Joint submission information from the secondary submitter consisting of the percentage of formulation required pursuant to § 705.15(b)(1)(i) and (ii).

Because signatures are required by each party of a joint submission, each party must register with CDX and complete their own sections of the same report. The reporting tool will match both submissions based upon the unique ID number sent by the manufacturer (including importer) to notify the secondary submitter of the partial section 8(a)(7) submission. Suppliers do not have access to any of the information submitted to EPA by the manufacturer (except the manufacturer's identity and contact information and the submitted trade name or chemical identifier) . Likewise, manufacturers cannot see the information that the supplier reports to EPA.

This way, the confidentiality of information for all submitters is protected. The information provided by both submitters will be combined and processed as one joint submission once they are received by EPA.

NOTE: In the event that a manufacturer (including importer) actually knows or can reasonably ascertain the chemical identity (e.g., the CASRN or Accession Number) of a chemical substance subject to section 8(a)(7) reporting, the manufacturer (including importer) must provide that information irrespective of a supplier's confidentiality claims. If

such a primary submitter wishes to claim the chemical identity as confidential, to do so they must check the CBI box and provide upfront substantiation as described in 4.5.1 of this chapter.

5. How to Obtain Copies of Documents Cited in This Instructions Document

5.1 Obtaining Copies of the TSCA Rules

The section 8(a)(7) rule, *40 CFR 705*, is available on the U.S. Government Publishing Office website, *www.ecfr.gov*.

You may also contact the TSCA Hotline by telephone at (202) 554-1404 or by email tsca-hotline@epa.gov for assistance.

5.2 Obtaining Copies of Other Information Materials

EPA has developed documents to provide additional information on submitting information for this data call. Except where otherwise noted, materials are available on the section 8(a)(7) website at *https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-section-8a7-reporting-and- recordkeeping*. In addition to materials developed specifically for section 8(a)(7) reporting, some materials developed for TSCA more broadly or for CDR reporting are also applicable to reporting under this data call.

Reporting Electronically:

- Instructions on CDX registration: *CDX Online Registration User Guide*
- Some fact sheets Fact Sheets for CDR are relevant to section 8(a)(7) reporting. These fact sheets are available at *How To Report Under Chemical Data Reporting*. CDR fact sheets relevant to reporting under this data call include:
- *Reporting After Changes to Company Ownership or Legal Identity*
- *Imported Articles* (use this fact sheet as guidance in determining if your chemical substance is contained in an article; other items discussed in this fact sheet, such as references to reporting thresholds and polymer exemption, do not apply to this data call)

Appendix A. Glossary of Terms

The definitions and descriptions of terms used in section 8(a)(7) reporting provided below are taken from 40 CFR Part 711 unless otherwise noted.

Act means the Toxic Substances Control Act, as amended, 15 U.S.C. 2601 *et seq*.

Administrator means the Administrator of the Environmental Protection Agency. (See TSCA 3(1))

Article means a manufactured item (1) which is formed to a specific shape or design during manufacture, (2) which has end-use function(s) dependent in whole or in part upon its shape or design during end use, and (3) which has either no change of chemical composition during its end use or only those changes of composition which have no commercial purpose separate from that of the article, and that result from a chemical reaction that occurs upon end use of other chemical substances, mixtures, or articles; except that fluids and particles are not considered articles regardless of shape or design. (40 CFR 704.3)

Byproduct means a chemical substance produced without separate commercial intent during the manufacture, processing, use, or disposal of another chemical substance(s) or mixture(s). (40 CFR 704.3)

Central Data Exchange (CDX) means EPA's centralized electronic document receiving system, or its successors, including associated instructions for registering to submit electronic documents.

Chemical Information Submission System (CISS) means EPA's electronic, web-based reporting tool for the completion and submission of data, reports, and other information, or its successors.

Chemical substance means any organic or inorganic substance of a particular molecular identity, including any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and any element or uncombined radical. "Chemical substance" does *not* include:

(1) Any mixture;

(2) Any pesticide (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act) when manufactured, processed, or distributed in commerce for use as a pesticide;

(3) Tobacco or any tobacco product;

(4) Any source material, special nuclear material, or byproduct material (as such terms are defined in the Atomic Energy Act of 1954 [42 U.S.C. 2011 et seq.] and the regulations issued under such Act);

(5) Any article the sale of which is the subject to the tax imposed by section 4181 of the Internal Revenue Code of 1986 [26 U.S.C. 4181] (determined without regard to any

exemptions from such tax provided by section 4182 or 4221 or any other provision of such Code) and any component of such an article (limited to shot shells, cartridges, and components of shot shells and cartridges); and

(6) Any food, food additive, drug, cosmetic, or device (as such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321]) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device. (See TSCA 3(2))

Commerce means trade, traffic, transportation, or other commerce: (A) between a place in a State and any place outside of such State, or (B) which affects trade, traffic, transportation, or commerce described in clause (A). (TSCA 3(3))

Commercial use means the use of a chemical substance or a mixture containing a chemical substance (including as part of an article) in a commercial enterprise providing saleable goods or services.

Consumer use means the use of a chemical substance or a mixture containing a chemical substance (including as part of an article) when sold to or made available to consumers for their use.

Customs territory of the United States, as referenced in TSCA section 3 and defined in general note 2 of the Harmonized Tariff Schedule of the United States, includes only the States, the District of Columbia, and Puerto Rico.

Distribute in commerce and distribution in commerce, when used to describe an action taken with respect to a chemical substance or mixture or article containing a substance or mixture mean to sell, or the sale of, the substance, mixture, or article in commerce; to introduce or deliver for introduction into commerce, or the introduction or delivery for introduction into commerce of, the substance, mixture, or article; or to hold, or the holding of, the substance, mixture, or article after its introduction into commerce. (TSCA 3(5))

Environmental or health effects information means any information of any effect of a chemical substance or mixture containing a chemical substance on health or the environment or on both. This includes all health and safety studies.

(1) Not only is information that arises as a result of a formal, disciplined study included, but other information relating to the effects of a chemical substance or mixture containing a chemical substance on health or the environment is also included. Any information that bears on the effects of a chemical substance on health or the environment would be included.

(2) Examples are:

(i) Long- and short-term tests of mutagenicity, carcinogenicity, or teratogenicity; data on behavioral disorders; dermatoxicity; pharmacological effects;

mammalian absorption, distribution, metabolism, and excretion; cumulative, additive, and synergistic effects; and acute, subchronic, and chronic effects.

(ii) Tests for ecological or other environmental effects on invertebrates, fish, or other animals, and plants, including: Acute toxicity tests, chronic toxicity tests, critical life-stage tests, behavioral tests, algal growth tests, seed germination tests, plant growth or damage tests, microbial function tests, bioconcentration or bioaccumulation tests, and model ecosystem (microcosm) studies.

(iii) Assessments of human and environmental exposure, including workplace exposure, and impacts of a particular chemical substance or mixture containing a chemical substance on the environment, including surveys, tests, and studies of: Biological, photochemical, and chemical degradation; structure/activity relationships; air, water, and soil transport; biomagnification and bioconcentration; and chemical and physical properties, e.g., boiling point, vapor pressure, evaporation rates from soil and water, octanol/water partition coefficient, and water solubility.

(iv) Monitoring data, including but not limited to when they have been aggregated and analyzed to measure the exposure of humans or the environment to a chemical substance or mixture containing a chemical substance. (40 CFR 705.15)

EPA means the United States Environmental Protection Agency. (40 CFR 704.3)

Health and safety studies means any study of any effect of a chemical substance or mixture on health or the environment or on both, including underlying information and epidemiological studies, studies of occupational exposure to a chemical substance or mixture, toxicological, clinical, and ecological studies of a chemical substance or mixture containing a chemical substance, and any test performed under TSCA. [15 U.S.C. 2602(8)]

Highest-level Parent Company means the highest-level company of the site's ownership hierarchy as of the start of the submission period during which data are being reported according to the following instructions. The highest-level U.S. parent company is located within the United States while the highest-level foreign parent company is located outside the United States. The following rules govern how to identify the highest-level U.S. parent company and highest-level foreign parent company (if applicable):

(1) If the site is entirely owned by a single U.S. company that is not owned by another company, that single company is the U.S. parent company.

(2) If the site is entirely owned by a single U.S. company that is, itself, owned by another U.S.-based company (e.g., it is a division or subsidiary of a higher-level company), the highest- level domestic company in the ownership hierarchy is the United States parent company. If there is a higher-level parent company that is outside of the United States, the highest-level foreign company in the ownership hierarchy is the foreign parent company.

(3) If the site is owned by more than one company (e.g., company A owns 40 percent, company B owns 35 percent, and company C owns 25 percent), the company with the largest ownership interest in the site is the parent company. If a higher-level company in the ownership hierarchy owns more than one ownership company, then determine the entity with the largest ownership by considering the lower-level ownerships in combination (e.g., corporation X owns companies B and C, for a total ownership of 60 percent for the site).

(4) If the site is owned by a 50:50 joint venture or a cooperative, the joint venture or cooperative is its own parent company. If the site is owned by a U.S. joint venture or cooperative, the highest level of the joint venture or cooperative is the U.S. parent company. If the site is owned by a joint venture or cooperative outside the United States, the highest level of the joint venture or cooperative outside the United States is the foreign parent company.

(5) If the site is federally owned, the highest-level federal agency or department is the U.S. parent company.

(6) If the site is owned by a non-federal public entity, that entity (such as a municipality, State, or tribe) is the U.S. parent company.

Importer means

(1) any person who imports any chemical substance or any chemical substance as part of a mixture or article into the customs territory of the United States, and includes:

  (i) the person primarily liable for the payment of any duties on the merchandise, or

  (ii) an authorized agent acting on his/her behalf.

(2) Importer also includes, as appropriate:

  (i) The consignee.

  (ii) The importer of record.

  (iii) The actual owner if an actual owner's declaration and superseding bond have been filed in accordance with 19 CFR 141.20.

  (iv) The transferee, if the right to draw merchandise in a bonded warehouse has been transferred in accordance with subpart C of 19 CFR part 144.

(3) For the purposes of this definition, the customs territory of the United States consists of the 50 States, Puerto Rico, and the District of Columbia. (40 CFR 704.3)

Impurity means a chemical substance which is unintentionally present with another chemical substance. (40 CFR 704.3)

Industrial function means the intended physical or chemical characteristic for which a chemical substance or mixture is consumed as a reactant; incorporated into a formulation, mixture, reaction product, or article; repackaged; or used.

Industrial use means use at a site at which one or more chemical substances or mixtures are manufactured (including imported) or processed.

Intended for use by children means the chemical substance or mixture is used in a product that is specifically intended for use by children age 14 or younger. A chemical substance or mixture is intended for use by children when the submitter answers "yes" to at least one of the following questions for the product into which the submitter's chemical substance or mixture is incorporated:

(1) Is the product commonly recognized (i.e., by a reasonable person) as being intended for children aged 14 or younger?

(2) Does the manufacturer of the product state through product labeling or other written materials that the product is intended or will be used by children age 14 or younger?

(3) Is the advertising, promotion, or marketing of the product aimed at children age 14 or younger?

Intermediate means any chemical substance that is consumed, in whole or in part, in chemical reactions used for the intentional manufacture of other chemical substances or mixtures, or that is intentionally present for the purpose of altering the rates of such chemical reactions. (40 CFR 704.3)

Known to or reasonably ascertainable by means all information in a person's possession or control, plus all information that a reasonable person similarly situated might be expected to possess, control, or know. (40 CFR 704.3)

Manufacture means to manufacture, produce, or import, for commercial purposes. Manufacture includes the extraction, for commercial purposes, of a component chemical substance from a previously existing chemical substance or complex combination of substances. A chemical substance is co-manufactured by the person who physically performs the manufacturing and the person contracting for such production when that chemical substance, manufactured other than by import, is: (1) produced exclusively for another person who contracts for such production, and (2) that other person dictates the specific identity of the chemical substance and controls the total amount produced and the basic technology for the manufacturing process. [15 U.S.C. 2602(9)]

Manufacturer means a person who manufactures a chemical substance.

Manufacture for commercial purposes means: (1) to import, produce, or manufacture with the purpose of obtaining an immediate or eventual commercial advantage for the

manufacturer, and includes among other things, such “manufacture” of any amount of a chemical substance or mixture:

(i) For commercial distribution, including for test marketing.

(ii) For use by the manufacturer, including use for product research and development, or as an intermediate.

(2) Manufacture for commercial purposes also applies to substances that are produced coincidentally during the manufacture, processing, use, or disposal of another substance or mixture, including both byproducts that are separated from that other substance or mixture and impurities that remain in that substance or mixture. Such byproducts and impurities may, or may not, in themselves have commercial value. They are nonetheless produced for the purpose of obtaining a commercial advantage since they are part of the manufacture of a chemical product for a commercial purpose. (40 CFR 704.3)

Master Inventory File means EPA's comprehensive list of chemical substances which constitute the Chemical Substances Inventory compiled under section 8(b) of the Act. It includes substances reported under 40 CFR Part 710 and substances reported under Part 720 for which a Notice of Commencement of Manufacture or Import has been received under § 720.120.

Microorganism means any combination of chemical substances that is a living organism and that meets the definition of microorganism at 40 CFR 725.3. Any chemical substance produced from a living microorganism is reportable under the CDR regulation unless otherwise excluded.

Mixture means any combination of two or more chemical substances if the combination does not occur in nature and is not, in whole or in part, the result of a chemical reaction; except that such term does include any combination which occurs, in whole or in part, as a result of a chemical reaction if none of the chemical substances comprising the combination is a new chemical substance and if the combination could have been manufactured for commercial purposes without a chemical reaction at the time the chemical substances comprising the combination were combined. (TSCA 3(10))

Naturally occurring substance is any chemical substance which is naturally occurring and: (1) which is (i) unprocessed or (ii) processed only by manual, mechanical, or gravitational means, by dissolution in water, by flotation, or by heating solely to remove water; or (2) which is extracted from air by any means. (40 CFR 710.4(b))

Non-isolated intermediate means any intermediate that is not intentionally removed from the equipment in which it is manufactured, including the reaction vessel in which it is manufactured, equipment which is ancillary to the reaction vessel, and any equipment through which the substance passes during a continuous flow process, but not including tanks or other vessels in which the substance is stored after its manufacture. (40 CFR 704.3)

Parent Company is a company that owns or controls another company. (40 CFR 704.3)

Per- and polyfluoroalkyl substances or **PFAS**, means any chemical substance or mixture containing a chemical substance that structurally contains at least one of the following three sub-structures:

1. R-(CF_2)-CF(R')R'', where both the CF_2 and CF moieties are saturated carbons
2. R-CF_2OCF_2-R', where R and R' can either be F, O, or saturated carbons
3. $CF_3C(CF_3)$R'R'', where R' and R"" can either be F or saturated carbons. (40 CFR 705.15)

Person means any individual, firm, company, corporation, joint venture, partnership, sole proprietorship, association, or any other business entity; any State or political subdivision thereof, or any municipality; any interstate body; and any department, agency, or instrumentality of the Federal government. (40 CFR 704.3)

Polymer means any chemical substance described with the word fragments "*polym*", "*alkyd", or "oxylated" in the Chemical Abstracts (CA) Index Name in the Master Inventory File, where the asterisk (*) in the listed word fragments indicates that any sets of characters may precede, or follow, the character string defined. Polymers also include any chemical substance which is identified in the Master Inventory File as siloxane(s) and silicone(s), silsesquioxane(s), a protein (albumin, casein, gelatin, gluten, hemoglobin), an enzyme, a polysaccharide (starch, cellulose, or gum), rubber, or lignin. The polymer exclusion does not apply to a polymeric substance that has been hydrolyzed, depolymerized, or otherwise chemically modified, except in cases where the intended product of this reaction is totally polymeric in structure.

Possession or control means in possession or control of the submitter, or of any subsidiary, partnership in which the submitter is a general partner, parent company, or any company or partnership which the parent company owns or controls, if the subsidiary, parent company, or other company or partnership is associated with the submitter in the research, development, test marketing, or commercial marketing of the chemical substance in question. (A parent company owns or controls another company if the parent owns or controls 50 percent or more of the other company's voting stock. A parent company owns or controls any partnership in which it is a general partner). Information is included within this definition if it is:

(1) In files maintained by submitter's employees who are:

  (i) Associated with research, development, test marketing, or commercial marketing of the chemical substance in question.

  (ii) Reasonably likely to have such data.

(2) Maintained in the files of other agents of the submitter who are associated with research, development, test marketing, or commercial marketing of the chemical substance in question in the course of their employment as such agents. (40 CFR 705.15)

Process means to process for commercial purposes. (40 CFR 704.3)

Process for commercial purposes means the preparation of a chemical substance or mixture after its manufacture for distribution in commerce with the purpose of obtaining an immediate or eventual commercial advantage for the processor. Processing of any amount of a chemical substance or mixture is included in this definition. If a chemical substance or mixture containing impurities is processed for commercial purposes, then the impurities also are processed for commercial purposes. (40 CFR 704.3)

Processor means any person who processes a chemical substance or mixture. (40 CFR 704.3)

Reasonably likely to be exposed means an exposure to a chemical substance which, under foreseeable conditions of manufacture (including import), processing, distribution in commerce, or use of the chemical substance, is more likely to occur than not to occur. Such exposures would normally include, but would not be limited to, activities such as charging reactor vessels, drumming, bulk loading, cleaning equipment, maintenance operations, materials handling and transfers, and analytical operations. Covered exposures include exposures through any route of entry (inhalation, ingestion, skin contact, absorption, etc.), but excludes accidental or theoretical exposures.

Repackaging means the physical transfer of a chemical substance or mixture, as is, from one container to another container or containers in preparation for distribution of the chemical substance or mixture in commerce.

Reportable chemical substance means a chemical substance described in § 711.5.

Research and development (R&D) means activities intended solely as scientific experimentation, research, or analysis. R&D focuses on the analysis of the chemical or physical characteristics, the performance, or the production characteristics of a chemical substance, a mixture containing the substance, or an article. R&D encompasses a wide range of activities which may occur in a laboratory, pilot plant, commercial plant outside the research facility, or at other sites appropriate for R&D. General distribution of chemical substances to consumers does not constitute R&D. (40 CFR 705.15)

Site means a contiguous property unit. Property divided only by a public right-of-way shall be considered one site. More than one plant may be located on a single site.

(a) For chemical substances manufactured under contract, i.e., by a co-manufacturer, the site is the location where the chemical substance is physically manufactured.

(b) The site for an importer who imports a chemical substance described in § 711.5 is the U.S. site of the operating unit within the person's organization that is directly responsible for importing the substance. The import site, in some instances, may be the organization's headquarters in the United States. If there is no such operating unit or headquarters in the United States, the site address for the importer is the

United States address of an agent acting on behalf of the importer who is authorized to accept service of process for the importer.

(c) For portable manufacturing units sent out to different locations from a single distribution center, the distribution center shall be considered the site.

Site-limited means a chemical substance is manufactured and processed only within a site and is not distributed for commercial purposes as a substance or as part of a mixture or article outside the site. Imported substances are never site-limited. Although a site-limited chemical substance is not distributed for commercial purposes outside the site at which it is manufactured and processed, the substance is considered to have been manufactured and processed for commercial purposes.

Small government means the government of a city, county, town, township, village, school district, or special district with a population of less than 50,000. (40 CFR 704.3)

Small manufacturer means a manufacturer (including importer) that meets either of the following standards:

(1) *First standard.* A manufacturer (including importer) of a substance is small if its total annual sales, when combined with those of its parent company (if any), are less than $120 million. However, if the annual production or importation volume of a particular substance at any individual site owned or controlled by the manufacturer or importer is greater than 45,400 kilograms (100,000 lbs), the manufacturer (including importer) will not qualify as small for purposes of reporting on the production or importation of that substance at that site, unless the manufacturer (including importer) qualifies as small under standard (2) of this definition.

(2) *Second standard.* A manufacturer (including importer) of a substance is small if its total annual sales, when combined with those of its parent company (if any), are less than $12 million, regardless of the quantity of substances produced or imported by that manufacturer (including importer). (40 CFR 704.3)

Small quantities solely for research and development (or "small quantities solely for purposes of scientific experimentation or analysis or chemical research on, or analysis of, such substance or another substance, including such research or analysis for the development of a product") means quantities of a chemical substance manufactured, imported, or processed or proposed to be manufactured, imported, or processed solely for research and development that are no greater than reasonably necessary for such purposes. (40 CFR 704.3)

State means any State of the United States, the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, Guam, the Canal Zone, American Samoa, the Northern Mariana Islands, or any other territory or possession of the United States. (TSCA 3(16))

Submission period means the period in which data are submitted to EPA.

United States, when used in the geographic sense, means all of the States. (TSCA3(17))

Use means any utilization of a chemical substance or mixture that is not otherwise covered by the terms *manufacture* or *process*. Relabeling or redistributing a container holding a chemical substance or mixture where no repackaging of the chemical substance or mixture occurs does not constitute use or processing of the chemical substance or mixture.

Worker means someone at a site of manufacture, import, or processing who performs work activities near sources of a chemical substance or mixture or directly handles the chemical substance or mixture during the performance of work activities. (40 CFR 705.15)

Appendix B. Key Comparisons between Section 8(a)(7) Data Call and CDR

This PFAS data call is promulgated under TSCA section 8(a)(7) and has many similarities to Chemical Data Reporting (CDR) required under TSCA section 8(a)(1). You or someone else at your site or company may have previously reported to CDR. However, it is important to note that there are certain differences between section 8(a)(7) reporting and reporting under CDR. You should review the final rule in 40 CFR 705 as well as this document to ensure you are reporting correctly. To assist you, this section outlines key differences between section 8(a)(7) reporting and reporting under CDR. Important differences to consider include:

- Absence of certain reporting exemptions and reporting thresholds that exist under CDR
- Differences in what data elements are to be reported
- Timeframe (years covered by the rule)
- Considerations for claiming information as confidential business information (CBI)
- Availability of streamlined reporting options in certain manufacturing scenarios

Reporting Exemptions

PFAS section 8(a)(7) reporting does not provide any exemptions. Do not assume you qualify for a section 8(a)(7) exemption because you qualify for a CDR exemption. Review Section 2 of this document for additional guidance on determining if you are required to report. For example, CDR reporters are not required to report for small manufacture/import quantities, chemicals imported as part of an article, or chemicals manufactured as byproducts that meet exemption requirements under 711.10(c), 711.10 (d)(1), or 711.10(d)(2). ***No such exemptions apply to section 8(a)(7) reporting – you may be required to submit a section 8(a)(7) report even if one of these, or any other, CDR exemption applies to your chemical substance.***

CDR exemptions that ***do not apply*** to PFAS Section 8(a)(7) reporting include, but are not limited to, exemptions for: articles containing PFAS (including imported articles containing PFAS such as articles containing PFAS as part of surface coatings), byproducts, impurities, polymers, and non-isolated intermediates.

Reported Data Elements

Data to be reported under section 8(a)(7) include some fields comparable to data reporting under CDR and some additional data. For fields comparable to CDR reporting, note that there may be differences between requirements for how to report to this data call compared to CDR reporting. In particular, lists of codes (such as codes for reporting industrial uses) may differ from the codes your site has used to report to CDR in the past. Additional data to be reported includes information on byproducts, environmental and health effects, worker exposure during industrial and commercial use, and disposal.

Covered Timeframe

This data call covers activities occurring from January 1, 2011, through December 31, 2022 (i.e., the end of the last calendar year prior to the effective date of this rule), a period of 12 years. Unlike CDR reporting, all years are treated equally for purposes of this data call; there is no "principal reporting year," and the same data elements must be reported for each year. The reporting software allows you to select a subset of years to report on if you did not manufacture the PFAS every year.

Considerations for CBI claims

Although the process of asserting CBI claims is similar to the process used for CDR reporting, there are some important differences. Review the section 8(a)(7) rule and this guidance when asserting CBI claims. It is your responsibility to ensure you are claiming and substantiating CBI claims **as required by the section 8(a)(7) rule**. If you fail to substantiate your CBI claims in accordance with the statute and applicable rules, EPA may make the information available to the public without further notice to you. However, EPA intends to publish a list of Accession numbers for which either no chemical identity CBI claim was asserted or the claim was denied as candidates for moving to the public Inventory and provide opportunity for other claimants of the chemical identity to appeal. Instructions for claiming and substantiating CBI claims are included in the instructions for each section. For additional information about how to answer substantiation questions, visit *www.epa.gov/tsca-cbi* on the EPA website.

Appendix C. Examples of PFAS covered by this rule

The requirements of this part apply to all chemical substances and mixtures that are PFAS, consistent with the definition of PFAS at § 705.3. A non-exhaustive list of PFAS is provided in EPA's CompTox Dashboard. The CompTox list includes all chemicals with known structures that meet the definition of PFAS for section 8(a)(7) reporting. The CompTox list includes all known chemicals, regardless of their TSCA Inventory status, and is updated as new chemicals are added to the database. The CompTox list does not include all polymers or chemicals with undefined (unknown or variable) structures, which may be covered by this rule. This list is also available via EPA's Substance Registry Service. An Excel® file of chemicals on the TSCA Inventory that meet the definition of PFAS is provided in the Additional Resources section of the PFAS 8(a)(7) website: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-section-8a7-reporting-and-recordkeeping#additional-resources. The Excel® file includes both chemicals with known structures as well as polymers and other chemicals with unknown or variable composition.

Note that this rule defines PFAS using a structural definition. While EPA is providing these lists to assist potentially affected entities with identifying reportable PFAS, manufacturers are advised that a chemical substance's omission from these lists does not necessarily mean it is not reportable under this rule. EPA notes that some possible reasons that a TSCA chemical substance that meets this rule's PFAS definition include: (1) being exempt from other TSCA reporting or notification requirements (e.g., certain byproducts, impurities, R&D substances); (2) a substance whose identity (even a generic identity) EPA cannot currently reveal due to confidential business information (CBI) protections.

Appendix D. Descriptions of Codes for Reporting Processing or Use Operations, Industrial Sectors, Function Categories, and Consumer and Commercial Product Categories

The following descriptions were developed by EPA to assist persons submitting information in response to 40 CFR 711.15(c) and reported in Part II.D of the section 8(a)(7) reporting. Table D-3Table D-3, Table D-4, Table D-5and Table D-6Table D-6 include crosswalks between OECD standardized codes to be used for section 8(a)(7) reporting and codes used for reporting to CDR.

For more information, see the Technical Support Document: "Harmonizing CDR Functional and Product codes with OECD Functional, Product, and Article Codes," located in the rulemaking record (EPA-HQ-OPPT-2018-0321).

Table D-1 provides the type of processing or use operation (TPU) codes with descriptions of the types of operations. These codes are used to report in Part II, Section B.

Table D-1. Type of Processing or Use Operation and Descriptions

Code	Type of Operation	Description
PC	Processing as a reactant	Chemical substance is used in chemical reactions for the manufacturing of another chemical substance or product.
PF	Processing—incorporation into formulation, mixture, or reaction product	Chemical substance is added to a product (or product mixture) prior to further distribution of the product.
PA	Processing—incorporation into article	Chemical substance becomes an integral component of an article distributed for industrial, trade, or consumer use.
PK	Processing—repackaging	Preparation of a chemical substance for distribution in commerce in a different form, state, or quantity. This includes transferring the chemical substance from a bulk container into smaller containers. This definition does not apply to sites that only relabel or redistribute the reportable chemical substance without removing the chemical substance from the container in which it is received or purchased.
U	Use—non-incorporative activities	Chemical substance is otherwise used (e.g., as a chemical processing or manufacturing aid).

Table D-2 provides a crosswalk between Industrial Sector (IS) codes used to report in Part II Section B with North American Industrial Classification System (NAICS) codes commonly used to classify businesses.

Table D-2. Industrial Sector (IS) Code Descriptions with NAICS Crosswalk

NAICS	IS Code	IS Title
11	IS1	Agriculture, Forestry, Fishing and Hunting
211	IS2	Oil and Gas Drilling, Extraction, and Support Activities
213		
212	IS3	Mining (except Oil and Gas) and Support Activities
22	IS4	Utilities
23	IS5	Construction
311	IS6	Food, beverage, and tobacco product manufacturing
312		
313	IS7	Textiles, apparel, and leather manufacturing
314		
315		
316		
321	IS8	Wood Product Manufacturing
322	IS9	Paper Manufacturing
323	IS10	Printing and Related Support Activities
32411	IS11	Petroleum Refineries
32412	IS12	Asphalt Paving, Roofing, and Coating Materials Manufacturing
324191	IS13	Petroleum Lubricating Oil and Grease Manufacturing
324199	IS14	All Other Petroleum and Coal Products Manufacturing
32511	IS15	Petrochemical Manufacturing
32512	IS16	Industrial Gas Manufacturing
32513	IS17	Synthetic Dye and Pigment Manufacturing
325182	IS18	Carbon Black Manufacturing
32518	IS19	All Other Basic Inorganic Chemical Manufacturing
325192	IS20	Cyclic Crude and Intermediate Manufacturing
32519	IS21	All Other Basic Organic Chemical Manufacturing
325211	IS22	Plastic Material and Resin Manufacturing

NAICS	IS Code	IS Title
325212	IS23	Synthetic Rubber Manufacturing
32522	IS24	Organic Fiber Manufacturing
3253	IS25	Pesticide, Fertilizer, and Other Agricultural Chemical Manufacturing
3254	IS26	Pharmaceutical and Medicine Manufacturing
32551	IS27	Paint and Coating Manufacturing
32552	IS28	Adhesive Manufacturing
3256	IS29	Soap, Cleaning Compound, and Toilet Preparation Manufacturing
32591	IS30	Printing Ink Manufacturing
32592	IS31	Explosives Manufacturing
325991	IS32	Custom Compounding of Purchased Resin
325992	IS33	Photographic Film Paper, Plate, and Chemical Manufacturing
325998	IS34	All Other Chemical Product and Preparation Manufacturing
3261	IS35	Plastics Product Manufacturing
3262	IS36	Rubber Product Manufacturing
327	IS37	Nonmetallic Mineral Product Manufacturing (includes clay, glass, cement, concrete, lime, gypsum, and other nonmetallic mineral product manufacturing)
331	IS38	Primary Metal Manufacturing
332	IS39	Fabricated Metal Product Manufacturing
333	IS40	Machinery Manufacturing
334	IS41	Computer and Electronic Product Manufacturing
335	IS42	Electrical Equipment, Appliance, and Component Manufacturing
336	IS43	Transportation Equipment Manufacturing
337	IS44	Furniture and Related Product Manufacturing
339	IS45	Miscellaneous Manufacturing
42	IS46	Wholesale and Retail Trade
44		
45		
48		
49		
51	IS47	Services
52		
53		
54		
55		

NAICS	IS Code	IS Title
56		
61		
62		
71		
72		
81		
92		
	IS48	Other (requires additional information)

Table D-3 provides the 2020 CDR Product Category codes (based on OECD harmonized codes) to be used for section 8(a)(7) reporting, with corresponding product category codes from 2016 CDR reporting. The 2016 CDR codes are provided only as a reference to assist you if your company has used these codes in past reporting. Do not use 2016 CDR codes for section 8(a)(7) reporting.

Table D-3. Product Category Codes

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Category**	**Code**	**Category**
Chemical Substances in Furnishing, Cleaning, Treatment Care Products			
CC101	Construction and building materials covering large surface areas including stone, plaster, cement, glass and ceramic articles; fabrics, textiles, and apparel	C101	Floor coverings
CC102	Furniture & furnishings including plastic articles (soft); leather articles	C102	Foam seating and bedding products
CC103	Furniture & furnishings including stone, plaster, cement,glass and ceramic articles; metal articles; or rubber articles	C103	Furniture and furnishings not covered elsewhere
CC104	Leather conditioner	C104	Fabric, textile, and leather products not covered elsewhere
CC105	Leather tanning, dye, finishing, impregnation and care products		
CC106	Textile (fabric) dyes		
CC107	Textile finishing and impregnating/surface treatment products		
CC108	All-purpose foam spray cleaner	C105	Cleaning and furnishing care products
CC109	All-purpose liquid cleaner/polish		
CC110	All-purpose liquid spray cleaner		
CC111	All-purpose waxes and polishes		
CC112	Appliance cleaners		
CC113	Drain and toilet cleaners (liquid)		
CC114	Powder cleaners (floors)		
CC115	Powder cleaners (porcelain)		
CC116	Dishwashing detergent (liquid/gel)	C106	Laundry and dishwashing products
CC117	Dishwashing detergent (unit dose/granule)		
CC118	Dishwashing detergent liquid (hand-wash)		
CC119	Dry cleaning and associated products		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Category**	**Code**	**Category**
CC120	Fabric enhancers		
CC121	Laundry detergent (unit-dose/granule)		
CC122	Laundry detergent (liquid)		
CC123	Stain removers		
CC124	Ion exchangers	C107	Water treatment products
CC125	Liquid water treatment products		
CC126	Solid/Powder water treatment products		
CC127	Liquid body soap	C108	Personal care products
CC128	Liquid hand soap		
CC129	Solid bar soap		
CC130	Air fresheners for motor vehicles	C109	Air care products
CC131	Continuous action air fresheners		
CC132	Instant action air fresheners		
CC133	Anti-static spray	C110	Apparel and footwear care products
CC134	Apparel finishing, and impregnating/surface treatment products		
CC135	Insect repellent treatment		
CC136	Pre-market waxes, stains, and polishes applied to footwear		
CC137	Post-market waxes, and polishes applied to footwear (shoe polish)		
CC138	Waterproofing and water-resistant sprays		
Chemical Substances in Construction, Paint, Electrical, and Metal Products			
CC201	Fillers and putties	C201	Adhesives and sealants
CC202	Hot-melt adhesives		
CC203	One-component caulks		
CC204	Solder		
CC205	Single-component glues and adhesives		
CC206	Two-component caulks		
CC207	Two-component glues and adhesives		
CC208	Adhesive/Caulk removers	C202	Paints and coatings

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Category**	**Code**	**Category**
CC209	Aerosol spray paints		
CC210	Lacquers, stains, varnishes and floor finishes		
CC211	Paint strippers/removers		
CC212	Powder coatings		
CC213	Radiation curable coatings		
CC214	Solvent-based paint		
CC215	Thinners		
CC216	Water-based paint		
CC217	Construction and building materials covering large surface areas, including wood articles	C203	Building/ construction materials - wood and engineered wood products
CC218	Construction and building materials covering large surface areas, including paper articles; metal articles; stone, plaster, cement, glass and ceramic articles	C204	Building/ construction materials not covered elsewhere
CC219	Machinery, mechanical appliances, electrical/electronic articles	C205	Electrical and electronic products
CC220	Other machinery, mechanical appliances,		
	electronic/electronic articles		
CC221	Construction and building materials covering large surface areas, including metal articles	C206	Metal products not covered elsewhere
CC222	Electrical batteries and accumulators	C207	Batteries
Chemical Substances in Packaging, Paper, Plastic, Toys, Hobby Products			
CC990	Non-TSCA use	C301	Food packaging
CC301	Packaging (excluding food packaging), including paper articles	C302	Paper products
CC302	Other articles with routine direct contact during normal use, including paper articles		
CC303	Packaging (excluding food packaging), including rubber articles; plastic articles (hard); plastic articles (soft)	C303	Plastic and rubber products not covered elsewhere
CC304	Other articles with routine direct contact during normal use including rubber articles; plastic articles (hard)		
CC305	Toys intended for children's use (and child dedicated articles), including fabrics, textiles, and apparel; or plastic articles (hard)	C304	Toys, playground, and sporting equipment
CC306	Adhesives applied at elevated temperatures	C305	

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Category**	**Code**	**Category**
CC307	Cement/concrete		Arts, crafts, and hobby materials
CC308	Crafting glue		
CC309	Crafting paint (applied to body)		
CC310	Crafting paint (applied to craft)		
CC311	Fixatives and finishing spray coatings		
CC312	Modelling clay		
CC313	Correction fluid/tape	C306	Ink, toner, and colorant products
CC314	Inks in writing equipment (liquid)		
CC315	Inks used for stamps		
CC316	Toner/Printer cartridge		
CC317	Liquid photographic processing solutions	C307	Photographic supplies, film, and photochemicals
Chemical Substances in Automotive, Fuel, Agriculture, Outdoor Use Products			
CC401	Exterior car washes and soaps	C401	Automotive care products
CC402	Exterior car waxes, polishes, and coatings		
CC403	Interior car care		
CC404	Touch up auto paint		
CC405	Degreasers	C402	Lubricants and greases
CC406	Liquid lubricants and greases		
CC407	Paste lubricants and greases		
CC408	Spray lubricants and greases		
CC409	Anti-freeze liquids	C403	Anti-freeze and de-icing products
CC410	De-icing liquids		
CC411	De-icing solids		
CC412	Lock de-icers/releasers		
CC413	Cooking and heating fuels	C404	Fuels and related products
CC414	Fuel additives		
CC415	Vehicular or appliance fuels		
CC416	Explosive materials	C405	Explosive materials
CC417	Agricultural non-pesticidal products	C406	Agricultural products (non-pesticidal)

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Category**	**Code**	**Category**
CC418	Lawn and garden care products	C407	Lawn and garden care products
Chemical Substances in Products not Described by Other Codes			
CC980	Other (specify)	C909	Other (specify)
CC990	Non-TSCA use	C980	Non-TSCA use

Table D-4Table D-4 provides the Function Category codes based on OECD harmonized codes to be used for section 8(a)(7) reporting, with corresponding Function Category codes from 2016 CDR reporting. The CDR codes are provided only as a reference to assist you if your company has used these codes in past reporting. Do not use CDR codes for section 8(a)(7) reporting.

Table D-4. Function Category Descriptions and Crosswalk: Section 8(a)(7) reporting and 2016-2020 CDR

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Description**	**Code**	**Description**
F001	Abrasives	U001	Abrasives
F002	Etching agent		
F003	Adhesion/cohesion promoter	U002	Adhesives and Sealant Chemicals
F004	Binder		
F005	Flux agent		
F006	Sealant (barrier)		
F007	Absorbent	U003	Adsorbents and Absorbents
F008	Adsorbent		
F009	Dehydrating agent (desiccant)		
F010	Drier		
F011	Humectant		
F012	Soil amendments (fertilizers)	U004	Agricultural Chemicals (non-pesticidal)
F013	Anti-adhesive/cohesive	U005	Anti-Adhesive Agents
F014	Dusting agent		
F015	Bleaching agent	U006	Bleaching Agents
F016	Brightener		
F017	Anti-scaling agent	U007	Corrosion inhibitors and antiscaling agents
F018	Corrosion inhibitor		
F019	Dye	U008	Dyes
F020	Fixing agent (mordant)		
F021	Hardener	U009	Fillers
F022	Filler		
F023	Anti-static agent	U010	Finishing agents
F024	Softener and conditioner		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Description**	**Code**	**Description**
F025	Swelling agent		
F026	Tanning agents not otherwise specified		
F027	Waterproofing agent		
F028	Wrinkle resisting agent		
F029	Flame retardant	U011	Flame retardants
F030	Fuel agents	U012	Fuels and fuel additives
F031	Fuel		
F032	Heat transferring agent	U013	Functional fluids (closed systems)
F033	Hydraulic fluids		
F034	Insulators		
F035	Refrigerants		
F036	Anti-freeze agent	U014	Functional fluids (open systems)
F037	Intermediate	U015	Intermediates
F038	Monomers		
F039	Ion exchange agent	U016	Ion exchange agents
F040	Anti-slip agent	U017	Lubricants and lubricant additives
F041	Lubricating agent		
F042	Deodorizer	U018	Odor agents
F043	Fragrance		
F044	Oxidizing agent	U019	Oxidizing/reducing agents
F045	Reducing agent		
F046	Photosensitive agent	U020	Photosensitive chemicals
F047	Photosensitizers		
F048	Semiconductor and photovoltaic agent		
F049	UV stabilizer		
F050	Opacifer	U021	Pigments
F051	Pigment		
F052	Plasticizer	U022	Plasticizers
F053	Plating agent	U023	Plating agents and surface treating agents
F054	Catalyst	U024	Process regulators

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Description**	**Code**	**Description**
F055	Chain transfer agent		
F056	Chemical reaction regulator		
F057	Crystal growth modifiers (nucleating agents)		
F058	Polymerization promoter		
F059	Terminator/Blocker		
F060	Processing aids, specific to petroleum production	U025	Processing aids, specific to petroleum production
F061	Antioxidant	U026	Processing aids, not otherwise listed
F062	Chelating agent		
F063	Defoamer		
F064	pH regulating agent		
F065	Processing aids not otherwise specified		
F066	Energy Releasers (explosives, motivepropellant)	U027	Propellants and blowing agents
F067	Foamant		
F068	Propellants, non-motive (blowing agents)		
F069	Cloud-point depressant	U028	Solids separation agents
F070	Flocculating agent		
F071	Flotation agent		
F072	Solids separation (precipitating) agent, not otherwise specified		
F073	Cleaning agent	U029	Solvents (for cleaning or degreasing)
F074	Diluent	U030	Solvents (which become part of product formulation or mixture)
F075	Solvent		
F076	Surfactant (surface active agent)	U031	Surface active agents
F077	Emulsifier		
F078	Thickening agent	U032	Viscosity adjustors
F079	Viscosity modifiers		
F080	Laboratory chemicals	U033	Laboratory chemicals
F081	Dispersing agent	U034	Paint additives and coating additives not described by other codes
F082	Freeze-thaw additive		
F083	Surface modifier		
F084	Wetting agent (non-aqueous)		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Description**	**Code**	**Description**
F085	Aerating and deaerating agents		
F086	Explosion inhibitor		
F087	Fire extinguishing agent		
F088	Flavoring and nutrient		
F089	Anti-redeposition agent		
F090	Anti-stain agent		
F091	Anti-streaking agent		
F092	Conductive agent		
F093	Incandescent agent		
F094	Magnetic element		
F095	Anti-condensation agent		
F096	Coalescing agent		
F097	Film former		
F098	Demulsifier		
F099	Stabilizing agent		
F100	Alloys	U999	Other (specify)
F101	Density modifier		
F102	Elasticizer		
F103	Flow promoter		
F104	Sizing agent		
F105	Solubility enhancer		
F106	Vapor pressure modifiers		
F107	Embalming agent		
F108	Heat stabilizer		
F109	Preservative		
F110	Anti-caking agent		
F111	Deflocculant		
F112	Dust suppressant		
F113	Impregnation agent		
F114	Leaching agent		
F115	Tracer		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.			
Column A: Section 8(a)(7) codes		**Column B: 2016 CDR codes**	
Code	**Description**	**Code**	**Description**
F116	X-ray absorber		
F999	Other (specify)		
NOTE: For codes F085 – F116, no comparable crosswalk code existed in 2016 CDR			

Table D-5Table D-5 provides the Consumer and Commercial Product Category codes based on OECD harmonized codes to be used for section 8(a)(7) reporting, with corresponding consumer and commercial product category codes from 2016 CDR reporting. The CDR codes are provided only as a reference to assist you if your company has used these codes in past reporting. Do not use CDR codes for section 8(a)(7) reporting.

Table D-5. Consumer and Commercial Product Category Descriptions and Crosswalk

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
Chemical Substances in Furnishing, Cleaning, Treatment Care Products				
CC101	Construction and building materials covering large surface areas including stone, plaster, cement, glass and ceramicarticles; fabrics, textiles, and apparel	Cement flooring, stone tile, mirrors, flooring or wall materials, carpets, rugs, tapestries	C101	Floor coverings
CC102	Furniture & furnishings includingplastic articles (soft); leather articles	Foam armchair, couch/sofa, mattress(adult), mattress (infant), mattress (child), sleeping bag, beanbag chair	C102	Foam seating and bedding products
CC103	Furniture & furnishings including stone, plaster, cement, glass and ceramic articles; metal articles; or rubber articles	Tables, chairs, benches, outdoor furniture, or furniture feet	C103	Furniture and furnishings not covered elsewhere
CC104	Leather conditioner	Products applied to leather surfaces to preserve and/or restore strength, appearance, and flexibility.	C104	Fabric, textile, and leather products not covered elsewhere
CC105	Leather tanning, dye, finishing, impregnation and care products	Products applied to the surfaces of leather articles to impart desirable properties.		
CC106	Textile (fabric) dyes	Products applied to impart color(s) to textiles.		
CC107	Textile finishing and impregnating/surface treatment products	Products applied to the surfaces of textiles to impart water or stain resistances, flame resistance, but not dyes.		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC108	All-purpose foam spray cleaner	Foams that are spray applied to surfaces such as countertops, tables, windows, and surfaces of appliances.	C105	Cleaning and furnishing care products
CC109	All-purpose liquid cleaner/polish	Liquids that are not spray applied and are applied to surfaces of furniture, silverware, sinks, tubs, carpeted floors, and hard-surface floors. Note: distinguish between “neat” and “dilute” products.		
CC110	All-purpose liquid spray cleaner	Liquids that are spray applied to surfaces such as countertops, tables, windows, and surfaces of appliances.		
CC111	All-purpose waxes and polishes	Waxes and other semi-solids that are not spray applied and are applied to the surfaces of furniture (generally wooden furniture) to improve shine and/or impart stain resistance.		
CC112	Appliance cleaners	Cleaners that are applied to the interior of appliances such as dishwashers, washing machines, electronic appliances, disposals, and ovens).		
CC113	Drain and toilet cleaners (liquid)	Liquids applied to toilets and/or drains that may remain in the sewer line for a time but ultimately go down the drain.		
CC114	Powder cleaners (floors)	Powders that are applied to carpets and rugs to clean or deodorize.		
CC115	Powder cleaners (porcelain)	Powders applied to sinks, showers, and tubs to remove dirt, soap scum, and mold.		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC116	Dishwashing detergent (liquid/gel)	Liquid cleaners added to dishwashing machines to remove food residue from dishes.	C106	Laundry and dishwashing products
CC117	Dishwashing detergent (unit dose/granule)	Powder or powder/liquid tablet cleaners added to washing machines to remove dirt from clothing and other textiles.		
CC118	Dishwashing detergent liquid (hand-wash)	Liquid cleaners added to sinks and combined with water to remove food residue from dishes.		
CC119	Dry cleaning and associated products	Products used to remove dirt from clothing and other textiles in non- aqueous cleaning processes.		
CC120	Fabric enhancers	Products which enhance fabrics. Examples include liquid products added to washing machines or sheetsadded to driers, bleach, film, lime and rust removers.		
CC121	Laundry detergent (unit-dose/granule)	Powder or powder/liquid tablet cleaners added to washing machinesto remove dirt from clothing and other textiles.		
C122	Laundry detergent (liquid)	Liquid cleaners added to washing machines to remove dirt from clothing and other textiles.		
CC123	Stain removers	Applied to clothing before addition to laundry machine to remove stains (can be gels, liquids, or spray applications).		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC124	Ion exchangers	Point of use filters which may be used by consumers in homes (e.g., refrigerator filters or pitcher filters) or in commercial and industrial settings to treat water for use in these processes.	C107	Water treatment products
CC125	Liquid water treatment products	Water treatment drops		
CC126	Solid/powder water treatment products	pH adjusters, filter media, water treatment tablets		
CC127	Liquid body soap	Liquid soap used for washing entire body.	C108	Personal care products
CC128	Liquid hand soap	Liquid soap used for washing hands.		
CC129	Solid bar soap	Solid soap used for washing hands and body.		
CC130	Air fresheners for motor vehicles	Aerosol spray and continuous action air products used to odorize or deodorize motor vehicles.	C109	Air care products
CC131	Continuous action air fresheners	Liquid, solid, gel diffuser, solid incense products and scented candle products that odorize or deodorize air in indoor environments.		
CC132	Instant action air fresheners	Aerosol spray and incense products that odorize or deodorize air in indoor environments.		
CC133	Anti-static spray	Spray applied to eliminate or reduce static electricity on apparel.	C110	Apparel and footwear care products
CC134	Apparel finishing, and impregnating/surface treatment products	Products applied to the surfaces of apparel to impart water or stain resistances, flame resistance, but not dyes.		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC135	Insect repellent treatment	Product applied to clothing to repel insects.		
CC136	Pre-market waxes, stains, and polishes applied to footwear	Waxes, stains, and polishes applied to footwear to impart water resistance, improve appearance and impart other desirable properties.		
CC137	Post-market waxes, and polishes applied to footwear (shoe polish)	Waxes and polishes applied to footwear.		
CC138	Waterproofing and water-resistant sprays	Spray applied to impart water resistance to apparel or footwear.		
<u>Chemical Substances in Construction, Paint, Electrical, and Metal Products</u>				
CC201	Fillers and putties	Highly malleable materials used to repair, smooth over, or fill minor cracks and holes in building surfaces.	C201	Adhesives and sealants
CC202	Hot-melt adhesives	Adhesives (supplied in solid cylindrical sticks and intended for small applications) designed to be melted and dispensed through an electric hot glue gun.		
CC203	One-component caulks	Caulks (sealants) which are premixed with their final product formulation. Examples include acrylic solvent-based, butyl solvent- based, latex water-based, silicone and polyurethane.		
CC204	Solder	Metal alloys melted down to permanently bond metal parts together. Commonly used in electronics, plumbing and sheet metal work.		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC205	Single-component glues and adhesives	Adhesives (packaged less than 8 ounces per bottle and intended for small amount per use applications such as bookbinding) which are premixed with their final product formulation. Product use and exposure to light, humidity, or temperature initiates chemical reaction and cure. Examples include anaerobic, cyanoacrylates, heat-cure, moisture-cure, radiation-cure, and silicones.		
CC206	Two-component caulks	Caulks (sealants) which are stored in two separate parts, generally a base and an activator. The activator is added to the base and mixed before application. Examples include epoxy-solvent based silicone and polyurethane.		
CC207	Two-component glues and adhesives	Adhesives (packaged in containers smaller than 8 ounces per container and intended for small applications) which are stored in two separate containers, generally a resin and a hardener which are then mixed together to initiate chemical reaction and cure. Examples include epoxies,		
		methyl methacrylates, silicon adhesives, and polyurethanes.		
CC208	Adhesive/caulk removers	Products applied to surfaces to unbind substances or remove sealants and to clean the underlying surface by softening adhesives, caulks and other glues so they can be removed.	C202	Paints and coatings

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC209	Aerosol spray paints	Pressurized one-component paint released with a propellant and spray applied as a fine mist.		
CC210	Lacquers, stains, varnishes and floor finishes	Liquids applied to surfaces such as floors, countertops, appliances, furnishings, decking, and patios to impart coloring or resistance to fade, scuffing, marking, or wear.		
CC211	Paint strippers/removers	Liquid product applied to surfaces to remove paint, coatings and other finishes and also to clean the underlying surface.		
CC212	Powder coatings	Dry powder coating that does not contain solvents and is cured under heat to create a coating film.		
CC213	Radiation curable coatings	Coatings designed to cure onto surface when exposed to radiation such as ultraviolet or electron beam radiation.		
CC214	Solvent-based paint	Paints that have been formulated to have a solvent as the vehicle.		
CC215	Thinners	Liquids to dilute paints and coatings to obtain suitable viscosity for paint application.		
CC216	Water-based paint	Paints that have been formulated to have water as the main vehicle.		
CC217	Construction and building materials covering large surface areas, including wood articles	Floor decking, claddings, toys outdoor equipment, walls, flooring	C203	Building/ construction materials - wood and engineered wood products

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC218	Construction and building materials covering large surface areas, including paper articles; metal articles; stone, plaster, cement, glass and ceramic articles	Construction and building materials; e.g. insulation panels, wall papers, roof sheets, drinking water pipes, sewer pipes, cement flooring, mirrors	C204	Building/ construction materials not covered elsewhere
CC219	Machinery, mechanical appliances, electrical/electronic articles	Refrigerators, washing machines, vacuum cleaners, computers, telephones, drills, saws, smoke detectors, thermostats, radiators	C205	Electrical and electronic products
CC220	Other machinery, mechanical appliances, electronic/electronic articles	Large-scale stationary industrial tools		
CC221	Construction and building materials covering large surface areas, including metal articles	Roof sheets, drinking water pipes, sewer pipes	C206	Metal products not covered elsewhere
CC222	Electrical batteries and accumulators	Batteries	C207	Batteries
Chemical Substances in Packaging, Paper, Plastic, Toys, Hobby Products				
CC990	Non-TSCA use	Items included under non-TSCA use include food contact articles, such as plastic wrap, plastic dinner ware, food storage, packaging containers.	C301	Food packaging
CC301	Packaging (excluding food packaging), including paper articles	Paper packaging	C302	Paper products
CC302	Other articles with routine direct contact during normal use, including paper articles	Nappies, feminine hygiene products, adult incontinence products, tissues, towels, toilet paper, newspapers, books, magazines, photographic paper and negatives		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC303	Packaging (excluding food packaging), including rubber articles; plastic articles (hard); plastic articles (soft)	Phone covers, personal tablet covers, styrofoam packaging, bubble wrap	C303	Plastic and rubber products not covered elsewhere
CC304	Other articles with routine direct contact during normal use including rubber articles; plastic articles (hard)	Gloves, boots, clothing, rubber handles, gear lever, steering wheels, handles, pencils, handheld device casing		
CC305	Toys intended for children's use (and child dedicated articles), including fabrics, textiles, and apparel; or plastic articles (hard)	Stuffed toys, blankets, comfort objects, dolls, car, animals, teething rings	C304	Toys, playground, and sporting equipment
CC306	Adhesives applied at elevated temperatures	Used at elevated temperatures to melt and apply adhesive which when cooled, hardens and adheres the two substances to one another. Examples include solder and hot-melt adhesive, see adhesive definitions.	C305	Arts, crafts, and hobby materials
CC307	Cement/concrete	Used to create and support structures and pathways.		
CC308	Crafting glue	Used to adhere two substances to one another, see adhesives definitions.		
CC309	Crafting paint (applied to body)	Used to add color to fingers, faces, or other body parts.		
CC310	Crafting paint (applied to craft)	Used to add color to crafting substances, see paints definitions.		
CC311	Fixatives and finishing spray coatings	Fixatives, shellacs, or other spray applied coatings intended to cover or hold other arts and crafts materials to a surface.		
CC312	Modelling clay	Used to mold or sculpt.		

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC313	Correction fluid/tape	Fluids used to cover up permanent ink so that corrections can be made.	C306	Ink, toner, and colorant products
CC314	Inks in writing equipment (liquid)	Liquids used in pens, markers, or other writing instruments.		
CC315	Inks used for stamps	Inks incorporated into stamp or ink pads used to apply ink to paper and other substrates.		
CC316	Toner/printer cartridge	Pigmented liquids, toners or powders contained in cartridges, bottles, or other dispensers used in printers and copy machines. This category includes printing inks for commercial applications.		
CC317	Liquid photographic processing solutions	Chemicals used in the stop bath, fixing bath, hardener, or stabilizer to develop photographs.	C307	Photographic supplies, film, and photochemicals
Chemical Substances in Automotive, Fuel, Agriculture, Outdoor Use Products				
CC401	Exterior car washes and soaps	Cleaning agents used to remove dirt and grime.	C401	Automotive care products
CC402	Exterior car waxes, polishes, and coatings	Used to increase the shine, add UV protection and scratch resistance to automotive paints, or provide waterproofing/resistant properties to windshields and automotive window glass.		
CC403	Interior car care	Cleaning agents used to remove stains from interior carpets and textiles, rubber, vinyl, or plastic.		
CC404	Touch up auto paint	Used to paint over scratches or cover up dent marks on automotive paints.		
CC405	Degreasers	Product that remove greases or oils from hard surfaces, machinery, or tools.	C402	Lubricants and greases

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
CC406	Liquid lubricants and greases	Liquids that reduce friction, heat generation and wear between surfaces.		
CC407	Paste lubricants and greases	Pastes that reduce friction, heat generation and wear between surfaces.		
CC408	Spray lubricants and greases	Sprays that reduce friction, heat generation and wear between surfaces.		
CC409	Anti-freeze liquids	Reduce the freezing point of surfaces.	C403	Anti-freeze and de-icing products
CC410	De-icing liquids	Reduce the freezing point of surfaces in order to remove ice.		
CC411	De-icing solids	Ice melting crystals, rock salts		
CC412	Lock de-icers/releasers	Applied within locks to remove ice so that doors can be opened.		
CC413	Cooking and heating fuels	Pressurized liquid fuels generally contained within metal containers and released directly into an appliance in a controlled way to prevent direct release.	C404	Fuels and related products
CC414	Fuel additives	Added to fuels to improve properties such as stability, corrosion, oxygenation, and octane rating.		
CC415	Vehicular or appliance fuels	Liquid fuels stored in containers and refilled into vehicles or appliances as needed.		
CC416	Explosive materials	Chemical substances capable of producing a sudden expansion usually accompanied by the production of heat and large changes in pressure upon initiation, that are intended for consumer or commercial use. Examples include pyrotechnics,	C405	Explosive materials

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
		high explosives and propellants, igniter, primer, initiatory, illuminants, smoke and decoy flares, and incendiaries.		
CC417	Agricultural non-pesticidal products	Products used to increase the productivity of crops, or aid in the harvesting of crops. Examples include fertilizers, colorants, and application aids, and soil amendments (e.g. products added to soil to adjust pH, retain water or alter other properties).	C406	Agricultural products (non-pesticidal)
CC418	Lawn and garden care products	Chemical substances contained in lawn, garden, outdoor or potted plant, and tree care products that are intended for consumer or commercial use should be reported under this code. Examples of lawn and garden care products include fertilizers and nutrient mixtures, soil amendments, mulches, pH adjustors, water retention beads, vermiculite, and perlite. Excludes any substance that is manufactured, processed, or distributed in commerce for use as a pesticide as defined in the Federal Insecticide, Fungicide, and Rodenticide Act.	C407	Lawn and garden care products
<u>Chemical Substances in Products not Described by Other Codes</u>				
CC980	Other (specify)	Provide description of use.	C909	Other (specify)
CC990	Non-TSCA use	Chemical substances contained in products intended for consumer or commercial use that are not regulated by TSCA should be reported under this code. Examples of products with non-TSCA uses include	C980	Non-TSCA use

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: Section 8(a)(7) codes			**Column B: 2016 CDR codes**	
Code	**Name**	**Description**	**Code**	**Name**
		pesticide, insecticide, rodenticide and fungicide formulations; food or drink for humans or animals; articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or animals; substances intended to be applied to the human body other than soap; any radioactive source material, special nuclear material, or byproduct material; pistols, revolvers, fire arms, or ammunition; and tobacco or tobacco products.		

Table D-6Table D-6 provides examples of products intended for use by children, including 2020 CDR (OECD-based) codes to be used for section 8(a)(7) reporting as well as 2016 CDR codes. This table is meant to help you identify products intended for use by children and may not include all products intended for use by children. The 2016 CDR codes in this table are provided only as a reference to assist you if your company has used these codes in past reporting. Do not use 2016 CDR codes for section 8(a)(7) reporting.

Table D-6. Examples of Products Intended for Use by Children

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: section 8(a)(7) codes		**Column B: 2016 CDR codes**		**Examples**
Codes	**Category**	**Code**	**Category**	
Chemical Substances in Furnishings, Cleanings, Treatment Care Products				
CC102	Furniture & furnishings including Plastic articles (soft); Leather articles	C102	Foam seating and bedding products	Child's car seat, children's sheets
CC103	Furniture & furnishings including Stone, plaster, cement, glass and ceramic articles; Metal articles; or Rubber articles	C103	Furniture and furnishings not covered elsewhere	Baby cribs, changing tables
CC106	Textile (fabric) dyes	C104	Fabric, textile, and leather products not covered elsewhere	Children's clothing
CC107	Textile finishing and impregnating/surface treatment products			Children's clothing, children's sheets, child's car seat
CC127	Liquid body soap	C108	Personal care products	Baby shampoo, children's bubble bath
Chemical Substances in Construction, Paint, Electrical and Metal Products				
CC219	Machinery, mechanical appliances, electrical/electronic articles	C205	Electrical and electronic products	Electronic games, remote control cars
CC222	Electrical batteries and accumulators	C207	Batteries	Batteries used in toys
Chemical Substances in Packaging, Paper, Plastic, Hobby Products				
CC302	Other articles with routine direct contact during normal use, including paper articles	C302	Paper products	Diapers, baby wipes, coloring books

Use column A for all reporting. Column B shows 2016 CDR codes, which may have been used for CDR reporting.				
Column A: section 8(a)(7) codes		**Column B: 2016 CDR codes**		**Examples**
Codes	**Category**	**Code**	**Category**	
CC305	Toys intended for children's use (and child dedicated articles), including Fabrics, textiles, and apparel; or Plastic articles (hard)	C304	Toys, playground, and sporting equipment	Pacifiers, toy trucks, dolls, toy cars, wagons, action figures, balls, swing sets, slides, skates, baseball gloves, kid's rake
CC306	Adhesives applied at elevated temperatures	C305	Arts, crafts, and hobby materials	Craft glue for a hot glue gun
CC308	Crafting glue			Craft glue
CC309	Crafting Paint (applied to body)			Chemicals used to add color to body paint, finger paints

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RESEARCH ARTICLE

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Ambient levels of PFOS and PFOA in multiple environmental media

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Abstract

Making remediation and risk management decisions for widely-distributed chemicals is a challenging aspect of contaminated site management. The objective of this study is to present an initial evaluation of the ubiquitous, ambient environmental distribution of poly- and perfluoroalkyl substances (PFAS) within the context of environmental decision-making at contaminated sites. PFAS are anthropogenic contaminants of emerging concern with a wide variety of consumer and industrial sources and uses that result in multiple exposure routes for humans. The combination of widespread prevalence and low screening levels introduces considerable uncertainty and potential costs in the environmental management of PFAS.

PFAS are not naturally-occurring, but are frequently detected in environmental media independent of site-specific (i.e., point source) contamination. Information was collected on background and ambient levels of two predominant PFAS, perfluorooctane sulfonate and perfluorooctanoate, in North America in both abiotic media (soil, sediment, surface water, and public drinking water supplies) and selected biotic media (human tissues, fish, and shellfish). The background or ambient information was compiled from multiple published sources, organized by medium and concentration ranges, and evaluated for geographical trends and, when available, also compared to health-based screening levels. Data coverage and quality varied from wide-ranging and well-documented for soil, surface water, and serum data to more localized and less well-documented for sediment and fish and shellfish tissues and some uncertainties in the data were noted. Widespread ambient soil and sediment concentrations were noted but were well below human health-protective thresholds for direct contact exposures. Surface water, drinking water supply waters (representing a combination of groundwater and surface water), fish and shellfish tissue, and human serum levels ranged from less than to greater than available health-based threshold values. This evaluation highlights the need for incorporating literature-based or site-specific background into PFAS site evaluation and decision-making, so that source identification, risk management, and remediation goals are properly focused and to also inform general policy development for PFAS management.

1 | INTRODUCTION

Poly- and perfluoroalkyl substances (PFAS) are a group of emerging anthropogenic compounds that are environmentally persistent and ubiquitous, and are used in a wide variety of consumer products and industrial applications requiring oil and water repellent properties such as polymers, surface protectors for leather, paper, clothing, food containers, upholstery, carpet, lubricants, fire-fighting foams, paper coatings, pharmaceuticals, and cosmetics (Agency for Toxic Substances and Disease Registry [ATSDR], 2015; U.S. Environmental Protection Agency [USEPA], 2016a, 2016b). Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are two of the most studied PFAS and have been documented to be present in both abiotic and biotic media worldwide (ATSDR, 2015; CONCAWE, 2016; Organisation for Economic Co-operation and Development [OECD], 2013; USEPA, 2016a, 2016b). The production of PFOS and PFOA was mostly discontinued in the early 2000s in many countries, but residual levels remain ubiquitous worldwide (ATSDR, 2015). Much attention is currently directed toward their investigation, evaluation, and remediation. Some risk-based screening benchmarks and preliminary remediation targets for selected PFAS are extremely low, especially for potable uses, on the order of nanograms per liter (ng/L) (New Jersey Drinking Water

Quality Institute, 2017; USEPA, 2016a, 2016b) and on the order of micrograms per kilogram (μg/kg) for soil leaching (USEPA, 2017). The combination of widespread prevalence and low screening levels introduces considerable uncertainty and potential costs in the characterization and remediation for PFAS at sites contaminated from known sources. The objective of this study is to understand the implications of the ubiquitous environmental distribution of PFAS on making risk management and remediation decisions at PFAS-contaminated sites.

PFAS are synthetic compounds and do not occur naturally in the environment, but are frequently detected in environmental media independent of site-specific sources (i.e., point sources). For example, atmospheric releases of PFAS and their precursors has led to downwind deposition of PFAS on the land surface that have ultimately migrated into drinking water aquifers while both atmospheric transport and ocean transport contribute to PFAS distribution in marine environments and food webs (ATSDR, 2015). The geographically wide-ranging contribution from this type of fate and transport mechanism is typically considered to be part of the ambient levels of PFAS in the environment since it cannot be traced directly to any single-point source.

PFAS are synthetic compounds and do not occur naturally in the environment, but are frequently detected in environmental media independent of site-specific sources (i.e., point sources).

Information was collected on background and ambient levels of PFAS in the United States and Canada in both abiotic media (soil, sediment, surface water, and public drinking water) and biotic media (human tissues, fish, and shellfish). Public drinking water supplies do not, in and of themselves, comprise an abiotic environmental medium. However, they represent a compilation of abiotic media sources that include surface water, groundwater, and groundwater under the direct influence of surface water (USEPA, 2007). Ambient data for groundwater were found to be very limited (too few to report herein) and ambient data for surface water were fairly localized, primarily focused on the Great Lakes Region and scattered studies mainly in the eastern region of the United States. For this reason, public drinking water data (described in more detail later), which provide much better spatial coverage of the United States than the available ambient data for surface water and groundwater, were evaluated to characterize freshwater resources with recognition of the fact that individual data points may represent PFAS concentrations originating from both point and nonpoint sources to groundwater and surface water entering public water systems. The uncertainties associated with the public drinking water data are detailed further in the Discussion section.

Biota data are particularly helpful for assessing dietary exposures by fish consumers because although bioaccumulation of long-chain PFAS, particularly PFOS, is well-documented, the mechanisms of PFAS bioaccumulation and biomagnification are not well understood and hence not easily estimated (Butt, Berger, Bossi, & Tomy, 2010). Information on ambient levels of PFAS in the environment represented by data collected from areas with no known sources of PFAS was compiled from federal and state publications and compilation documents, as well as the primary literature. The compiled data were organized by medium and PFAS, and then grouped into concentration ranges for purposes of evaluating geographical trends within each medium and between media. Ambient data were also compared to health advisory levels, when available, to evaluate the potential for background or ambient concentrations to exceed these risk-based values. Health-based advisory levels and screening levels are most readily available for soil, drinking water, and fish tissue. Variations in concentrations and exceedances of these advisory levels were evaluated in further detail.

These data are not meant to replace site-specific studies to establish statistically estimated background levels but rather to assist in defining the needs and scopes of more specific studies. For example, recognition of the ubiquitous distribution of polycyclic aromatic hydrocarbons (PAHs) eventually led to studies that established ambient concentrations of PAHs in northern and southern California soils and assisted in developing policy for remedial goals (California Department of Toxic Substances Control [DTSC], 2009; Environ, 2002a, 2002b). Based on this review, recommendations were developed for incorporating the background PFAS concept into policy and site management.

2 | MATERIALS AND METHODS

In this article, the terms "ambient" and "background" are used interchangeably to mean PFAS concentrations reported from locations and media with no known point source information. Similar to other anthropogenic chemicals that may be widely-distributed (e.g., polychlorinated biphenyls, PAHs), ambient levels of PFAS may be associated with multiple sources. For the purpose of this study, the reporting of ambient and background levels provides a useful perspective on interpreting the relative distributions of these chemicals in multiple media.

Identification and compilation of PFAS background data consisted of searching the wealth of existing PFAS literature available online. Given the current state of the science for PFAS research, with substantial numbers of new publications released every year during the last few years, the literature review conducted is not completely comprehensive. Efforts were made to gather as much readily available information as possible, and obtain primary literature articles referenced in secondary sources and guidance documents. However, it was necessary to limit the literature review in order to complete this evaluation within a reasonable timeframe, and the fact that other information may be available or may become available in the near future is a recognized uncertainty.

The following subsections describe the investigation for PFAS background data conducted for this study in more detail.

2.1 | Data of interest

2.1.1 | Regions

The focus of this study was to compile background data for PFAS in abiotic and biotic media from the United States and Canada. During the data compilation process, potential background data sources were noted for several other countries, including soil in China (Meng, Wang, Wang, Giesy, & Lu, 2013) and Mexico (Rankin, Mabury, Jenkins, & Washington, 2016; Strynar, Lindstrom, Nakayama, Egeghy, & Helfant, 2012), and human tissues, such as blood serum and umbilical cord blood, in Russia (Hanssen et al., 2013), Norway (Gützkow et al., 2011), Sweden (Kärrman et al., 2007), and Korea (Lee, Kim, Bae, & Yang, 2013). However, these data were not assessed and are not reported in this study.

Media that often comprise the focus of environmental remediation and human health risk assessment efforts were selected as the media of interest for this study.

2.1.2 | Media and analytes

Media that often comprise the focus of environmental remediation and human health risk assessment efforts were selected as the media of interest for this study. The abiotic media of interest were limited to soil, sediment, surface water, and drinking water from public utilities. As discussed previously, public drinking water data provide much better spatial coverage of the United States than surface water data and especially groundwater data. Drinking water data were evaluated to characterize freshwater resources, although individual data points may represent PFAS concentrations originating from point and nonpoint sources to surface water, groundwater, and groundwater under the influence of surface water entering public water systems. National drinking water PFAS concentrations from USEPA's third Unregulated Contaminant Monitoring Rule (UCMR3) requiring public water systems to monitor for these constituents were evaluated in this study. These data are collected at entry points to drinking water distribution systems that carry water from treatment plants to consumers or from sources to consumers when treatment is absent (USEPA, 2016b). Six PFAS are designated as List 1 Contaminants of this assessment monitoring program and are analyzed via USEPA Method 537: PFOS, PFOA, perfluorononanoic acid, perfluorohexane sulfonic acid, perfluoroheptanoic acid, and perfluorobutane sulfonate. The UCMR3 data were collected between 2013 and 2015. Given the numerous potential sources of PFAS to surface water and groundwater entering public water systems and reflected in the UCMR3 data, tracing all of these sources to point or nonpoint sources was not possible with the available data, as also noted by other researchers (Hu et al., 2016). Therefore, among the media evaluated in this study, drinking water is the only medium of exposure that represents both ambient and point source data, that is, does not represent only ambient levels of PFAS. These data provide valuable insight into drinking water concentrations and are designed to provide information for human exposure study by monitoring at the point of entry into distribution systems as opposed to pretreatment samples (USEPA, 2007). Herein, these data are considered to provide a gross spatial analysis of drinking water supplies that are receiving inputs of PFAS at various levels, regardless of source.

Biological tissues that have been documented as good indicators of PFAS exposure were also of particular interest. The biotic media of interest were limited to human blood (i.e., whole blood, serum, umbilical cord blood, and plasma) and fish and shellfish tissue. Potential background data sources were noted for other media, including household dust (Strynar & Linstrom, 2008), indoor air (Risk & Policy Analysts Limited [RPA] & BRE Environment, 2004), produce (OECD, 2002), and other biotic tissues such as semi-aquatic mammals (Giesy & Kannan, 2001), marine mammals (de Vos et al., 2008; Houde et al., 2006a, 2005; Houde, Martin, Letcher, Solomon, & Muir, 2006b; OECD, 2002), and birds (Giesy & Kannan, 2001; RPA & BRE Environment, 2004). However, these data were not assessed and are not reported in this study.

Although ambient data are available for several PFAS, only PFOS and PFOA were evaluated in this study, as the ambient datasets for these two compounds are the most abundant for the media of interest. Additionally, health advisory levels are available for PFOS and PFOA in some of these media, while advisory levels for most other PFAS have yet to be developed.

2.2 | Strategy for literature search

General online and strategic desktop searches were performed in the process of identifying and gathering PFAS background data. Specific search engines used include Google, Google Scholar, and Springer Link, as well as USEPA's EcoTox database. Technical journals and regulatory agency documents were reviewed to identify the most current publications with background data. A limited set of unpublished but relevant academic studies were also included. In some cases, data were reported in tables or text of secondary sources, in which case the primary literature sources cited were consulted for the background data whenever possible.

One of the most challenging aspects to the literature search was establishing the most effective key words to generate candidate PFAS background studies. For example, searching for "background" PFAS often resulted in studies based on evolving analytical methods for PFAS and the avoidance of background concentrations being reported as a consequence of cross-contamination in the laboratory. Regardless, "background" was one of the key words used in the internet search process as well as the following: ambient, reference, unimpacted, off-site, upgradient, upstream, nonoccupational exposure, unexposed population. Other relevant search terms were also used.

2.3 | Selection criteria for background or ambient data

Another challenge of this study was being able to differentiate between background data and data reflecting site impacts. Often this distinction was not readily apparent, and without the benefit of a full statistical evaluation of the study data to test for differences between sample populations, the study data were reviewed further to decide if they potentially represented background levels based on the description of the data in the report and through a visual analysis of the sample data. Qualitative criteria for inclusion of data included the following: statements by study authors regarding unimpacted sample locations (e.g., Rankin et al., 2016), selection of only reference or upstream locations from studies that included reference and impacted locations (e.g., Awad et al., 2011; Lanza, 2015; Lanza et al., 2002), and selection of locations from areas not known to support industrial facilities or uses (e.g., Strynar et al., 2012). Criteria for excluding data included the following: absence of statements or documentation regarding potential sources as well as clear statements regarding presumed or proven sources. Examples of excluded data included several publications that provided localized groundwater data without providing rationale for location selection or possible sources, and many publications that were focused on investigation of known source areas and releases.

The most current background conditions for PFAS reflecting environmental concentrations after the discontinued production of PFOS and PFOA were of primary interest to this study. Therefore, the most recent background data from studies spanning multiple years on a single project site, either presented in multiple publications or one publication, were retained for the background dataset. The overarching goal of this process was to incorporate the most current PFAS background data from each geographically distinct study site reported in the literature.

2.4 | Data preparation for analysis

Upon completion of the literature search and review process, the candidate sources of PFAS background data were identified and the most current data were entered into the dataset. The full electronic datasets were not readily available for most of the studies from which background data were gathered. In many cases only the summary statistics (e.g., minimum, maximum, mean) were available, and in some cases only one statistic was reported (i.e., geometric mean). For this reason, the background data gathered were accepted "as-is" and all potentially representative background levels for the media of interest were incorporated into the dataset of candidate values. This is another recognized uncertainty in the evaluation, as background levels (sometimes referred to as background threshold values) are more commonly represented by statistical limits, such as upper prediction limits (UPLs) or upper tolerance limits (USEPA, 2015a, 2015b, 2016c). These background statistics are then used to compare to the site maximum concentrations in order to identify constituents above background levels for purposes of site characterization (e.g., USEPA, 2002). When all site sample concentrations are below the selected background level, one may conclude that the samples collected at the site are likely within the background distribution, at a specified confidence level. To add to the transparency of the background data, the range of concentrations and either the arithmetic or geometric mean were reported in the results whenever possible.

The concentration units of the background data extracted from the literature were sometimes reported differently for the same medium. Therefore, it was necessary to convert the units for the data for each medium to make them consistent in the dataset. Conversion to the same units per medium allowed for comparison to each other in the evaluation of geographic concentration trends and patterns and for comparison to health advisory levels. For soil and sediment, the units were converted to μg/kg, corresponding to parts per billion. Dry weight (dw) values were preferred, but were not always available for sediment. For surface water and drinking water, the standardized units were ng/L, corresponding to parts per trillion. For human blood tissue samples, for example, serum, the standardized units were nanograms per milliliter (ng/mL), corresponding to parts per billion, and for fish and shellfish tissue samples the units were μg/kg. Wet weight (ww) fish and shellfish tissue data were desired for comparison to USEPA Regional Screening Levels (RSLs), however, most of the available shellfish tissue samples were available in dw.

The quality of the data was evaluated with respect to three key aspects: documentation of overall study design, documentation of quality assurance and quality control (QA/QC) procedures, and methodology for reporting nondetect values.

2.5 | Data quality review

The quality of the data was evaluated with respect to three key aspects: documentation of overall study design, documentation of quality assurance and quality control (QA/QC) procedures, and methodology for reporting nondetect values. Data quality for the studies retained for this review was highly variable, as would be expected. The results of the data quality evaluation are discussed further in the findings with respect to each medium since that, in itself, is an important part of the study results. However, a summary of data quality issues is included here. Overall, the most complete documentation of study design and QA/QC procedures was found for the more recent soil data (Lanza, 2015; Lanza et al., 2002; Rankin et al., 2016; Strynar et al., 2012) and drinking water (USEPA, 2016d). Documentation of study design and QA/QC procedures was noted for

a small subset of the already-limited sediment data (e.g., Awad et al., 2011), but was minimal or absent other for most sediment data (e.g., Health Protection Agency [HPA], 2012; OECD, 2002). However, all the sediment data were retained due to the limited amount of background or ambient sediment data found. The numerous surface water publication dates ranged from 2002 to 2011 and displayed a relatively robust level of documentation of sampling and analytical methods and QA/QC procedures, but with varying levels of discussion about the potential influence of local sources. Data that corresponded to unimpacted locations were selected from each publication. Similarly, human blood serum data (publication dates ranging from 2002 to 2017) and fish and shellfish data (publication dates ranging from 2002 to 2015) also included extensive discussion of QA/QC procedures but had varying levels of discussion about the rationale for selecting locations or sampled populations. Data that corresponded to specific locations with contamination sources were avoided when reported on an individual basis. In the unavoidable instance of reporting data that appeared to be anomalous (e.g., OECD, 2002), the potential for contamination and lower level of confidence is pointed out in the discussion.

A variety of proxies indicating a nondetect concentration were reported in the literature, such as method reporting limits, method detection limits, limits of quantification (LOQs), practical quantitation limit, etc. In the majority of the studies reviewed, nondetect data were only provided as one of these examples and, therefore, the nondetect data presented on the scatterplots is represented by a variety of nondetect measurements, including those reported as "0." However, the same symbol is used for all types of nondetect values in the distribution maps.

2.6 | Presentation of data

The completed background datasets for each medium are presented in the next section as geographically specific concentration ranges illustrated on a map of the United States and Canada and as scatter plots showing the range of actual concentrations reported for each location, when available. Concentration ranges were estimated for each study, or geographic location, by evaluating the geometric mean or and/or arithmetic mean depending on the statistics reported in the study. The geometric mean was calculated for drinking water from public utilities because all of the data were readily available electronically from one source (USEPA, 2016d). Given the wide range of reported concentrations in the datasets for most media, using the study-specific mean or an estimated mean based on the minimum and maximum detected concentrations was deemed most suitable for grouping the individual studies into general concentration ranges for the maps. For readability purposes of the maps, seven or less concentration ranges are provided per medium. This approach allowed for a gross comparison of PFAS background concentrations across the United States and Canada. Background distributions of PFOS and PFOA concentrations in groundwater are not described due to the extreme paucity of published data reflecting background conditions independent of any known local source.

Scatter plots were developed for a more refined illustration of the background data per location and also for a comparison of these data to available health advisory levels. The scatter plots present the minimum and maximum concentrations reported for each geographic area, as well as the geometric and/or arithmetic mean when reported. In some cases, the minimum and/or maximum concentrations reported for a certain location were nondetect concentrations.

For drinking water, the data were readily available and summary statistics were calculated with the actual data for this medium. The individual data points as well as the arithmetic and geometric means are shown on the scatter plot for drinking water.

USEPA health advisory level for PFOS and PFOA in drinking water of 70 ng/L is presented in the scatter plots for surface water and drinking water (USEPA, 2016a, 2016b). This lifetime health advisory level is based on protection of developmental toxicity in humans and is meant to be applied to the summation of PFOS and PFOA in a drinking water source. For soil and sediment, USEPA RSL Calculator Tool was used to generate a residential soil RSL of 1,260 μg/kg dw that is applicable to both PFOS and PFOA using the default residential input parameters provided in the tool (USEPA, 2017). Similarly, the default input parameters along with the current USEPA default fish ingestion rate of 22 grams per day used in the development of national ambient water quality criteria (USEPA, 2015c) were used to generate a fish tissue RSL of 75.8 μg/kg ww for the human fish consumption pathway that is applicable to both PFOS and PFOA. These ww-based fish tissue RSLs were compared to the background tissue data for fish and shellfish. In the absence of readily available risk-based screening levels for human blood serum, the Center for Disease Control and Prevention (CDC) blood levels of 21.7 ng/mL for PFOS and 5.7 ng/mL for PFOA were applied in the scatter plots to provide context to the background data gathered (ATSDR, 2017). These blood levels were developed through the National Health and Nutrition Examination Survey (NHANES) conducted by the CDC and represent levels at which 95 percent of the general population would be equivalent to or fall below. These blood levels are not indicative of health-based effects and simply represent concentrations detected in the specified sample population. The NHANES (2011–2012) measured the concentration of PFAS in the blood of a representative sample of the U.S. population (12 years of age and older).

The findings of this PFAS background investigation are presented later.

3 | FINDINGS AND DISCUSSION

The quality of the data was highly variable, as would be expected. With the exception of Rankin et al. (2016) and USEPA (2016d), there was little information regarding analytical methods, QA/QC procedures, and data quality in the majority of the sources.

For the Rankin et al. (2016) background soil study, the available data quality information was reviewed, such as field blanks to assess sample collection and transport procedures and process blanks to assess instrument sensitivity, and the decision made to retain all reported data. In Rankin et al. (2016), the mean concentrations of the 10 process blanks were subtracted from the soil concentrations reported. Regarding recovery, soil samples spiked with PFOA ranged from 77

EXHIBIT 1 Number of background data points for abiotic media

Medium	Habitat	Analyte	Geometric Mean	Arithmetic Mean	Median	Minimum	Maximum
Soil	Terrestrial	PFOA	0	31	0	0	7
Soil	Terrestrial	PFOS	0	31	0	0	7
Sediment	Freshwater	PFOA	0	0	0	1	1
Sediment	Freshwater	PFOS	0	0	0	4	4
Surface Water	Freshwater	PFOA	4	10	10	23	24
Surface Water	Freshwater	PFOS	3	10	11	27	27
Surface Water	Estuarine	PFOA	0	1	0	1	1
Surface Water	Estuarine	PFOS	0	1	0	1	1
Surface Water	Marine	PFOA	0	0	0	5	5
Surface Water	Marine	PFOS	0	0	0	5	5
Drinking Water	NA	PFOA	60	0	0	60	60
Drinking Water	NA	PFOS	60	0	0	60	60

to 132 percent with an average of 108 percent for all samples. Numerical concentrations were reported only if they exceeded the LOQ, while concentrations falling below the LOQ, but above the limit of detection (LOD), were reported as <LOQ. Concentrations below the LOD were reported as <LOD. There were eight samples associated with anomalous field or process blanks, which were used in the current evaluation as Rankin et al. (2016) did not find any unusual aspects associated with these samples upon further examination (collection and transportation practices were acceptable, etc.).

The UCMR data (USEPA, 2016d) were assumed to meet USEPA's data quality objectives and QA/QC requirements specified in the Federal Register (USEPA, 2007). No UCMR3 data were omitted from the current evaluation on the basis of data quality. All laboratories using USEPA drinking water methods under UCMR must demonstrate that they are capable of meeting data quality objectives at or below specified method reporting limits. Replicate analyses of at least seven fortified samples in reagent water must be performed at or below the method reporting limit for each analyte, and must be processed through the entire method procedure (i.e., including extraction, where applicable, and with all preservatives).

USEPA (2007) notes that the laboratory approval process is meant to establish a list of laboratories that have demonstrated their ability to perform the QA/QC requirements for UCMR methods. USEPA conducts a limited number of on-site laboratory audits to ensure these requirements continue to be met. Public water systems are also committed to contribute to data quality and are required to request and review the QC information associated with their UCMR data. Therefore, it is recognized that data quality issues may be present in the UCMR3 dataset, but these issues are assumed to represent only a small portion of the dataset given USEPA's rigorous procedures for selecting laboratories, designing QA/QC processes, and requiring each public water supply participating in the UCMR program to take responsibility for their data quality.

In spite of the selection criteria that made best efforts to select only data from background or ambient locations when possible, a major source of uncertainty that should be recognized with these data is that the influence of known or unknown sources of PFAS in the vicinity of the sample locations cannot be entirely discounted. The current search did not attempt to verify the absence of PFAS sources or confirm the contentions of the various studies as to unimpacted sample locations but did select data only from reference and unimpacted locations when they were so designated by the publication authors.

Exhibits 1 and 2 summarize the number of background data points identified for the primary abiotic and biotic media of interest.

The following sections describe these background data points in more detail.

3.1 | Abiotic media

The abiotic media of interest were limited to soil, sediment, surface water, and drinking water from public utilities, but other available media included household dust and indoor air.

Exhibit 3 presents a summary of the background data reported for soil and sediment, Exhibits 4 and 5 display the soil and sediment data on scatter plots, and Exhibits 6 and 7 illustrate the data as geographically specific concentration ranges presented on a map of North America.

3.1.1 | Soil

Two studies were identified (Rankin et al., 2016; Strynar et al., 2012) that contained background soil concentrations. All results for soil samples were reported in dw. The vast majority of the soil background data were extracted from Rankin et al. (2016), which reported sample results for perfluoroalkyl carboxylates (PFCAs) (C6 to C14), perfluoroalkyl sulfonates (PFSAs) (S6, S8, and S10), n:3 fluorotelomer acids and unsaturated fluorotelomer acids (n = 5 to 13 odd), and m:2 fluorotelomer acids and unsaturated fluorotelomer acids (n = 6 to 14 even). Every soil sample collected in this global study had quantifiable concentrations of at least three PFCAs. All samples from the United States and Canada had quantifiable concentrations of PFSAs, PFOS, PFOA, and PFHxA. In general, the most abundant PFCA and PFSA homologues in soil were PFOS and PFOA, with the highest concentrations being reported in Denmark and Japan, respectively (outside of the region of interest for this study).

EXHIBIT 2 Number of background data points for biotic media

Medium	Habitat	Analyte	Geometric mean	Arithmetic mean	Median	Minimum	Maximum
Blood serum	N/A	PFOA	25	24	15	23	23
Blood serum	N/A	PFOS	24	26	15	23	24
Liver	N/A	PFOA	0	0	0	1	1
Liver	N/A	PFOS	1	1	0	1	1
Plasma	N/A	PFOA	3	3	4	3	3
Plasma	N/A	PFOS	3	3	4	3	3
Umbilical cord blood	N/A	PFOA	1	3	2	2	2
Umbilical cord blood	N/A	PFOS	1	3	2	2	2
Whole blood	N/A	PFOA	0	2	2	2	2
Whole blood	N/A	PFOS	0	2	2	2	2
Fish liver	Freshwater	PFOA	0	5	0	10	10
Fish liver	Freshwater	PFOS	0	5	0	11	11
Fish liver	Marine	PFOA	0	2	0	2	2
Fish liver	Marine	PFOS	0	2	0	3	3
Whole fish	Freshwater	PFOA	0	6	0	4	4
Whole fish	Freshwater	PFOS	0	6	0	4	4
Whole fish	Marine	PFOA	0	1	0	2	2
Whole fish	Marine	PFOS	0	1	0	2	2
Bivalves	Freshwater	PFOA	0	0	0	3	3
Bivalves	Freshwater	PFOS	0	1	0	3	3
Bivalves	Marine	PFOA	0	1	0	1	1
Bivalves	Marine	PFOS	0	9	0	9	9
Crustacean	Freshwater	PFOA	0	0	0	6	6
Crustacean	Freshwater	PFOS	0	0	0	6	6
Crustacean	Marine	PFOA	0	1	0	1	1
Crustacean	Marine	PFOS	0	1	0	1	1
Fish muscle	Freshwater	PFOA	0	0	0	3	3
Fish muscle	Freshwater	PFOS	0	0	0	4	5
Fish eggs	Freshwater	PFOS	0	0	0	0	1
Fish muscle	Unknown	PFOS	0	0	0	0	1

All results from Rankin et al. (2016) were based on the mean of triplicate results from each location, whereas Strynar et al. (2012) reported the ten soils with the highest concentrations out of 60 total soil samples from six nations (United States of America, China, Japan, Norway, Greece, and Mexico). Only PFOS and PFOA data from the United States and Canada are reported herein.

As shown in Exhibit 3, 38 PFOS results ranged from 0.018 to 2.55 μg/kg. Forty results were obtained for PFOA, with values ranging from 0.059 to 1.84 μg/kg. These PFOS and PFOA soil samples were collected from 21 U.S. states, two U.S. territories, and two Canadian provinces. With the exception of a few data points in North Carolina, the spread in the soil background data for PFOS and PFOA falls within approximately two orders of magnitude difference between the minimum and maximum detections (Exhibits 4 and 5).

The same residential soil RSL was applied to both PFOS and PFOA soil RSL (1,260 μg/kg dw), and all background concentrations are well below the soil RSL, by two to three orders of magnitude. On a broad scale, the highest PFAS concentrations in soil are reported for the Eastern United States, with some other sporadic moderately high levels in soil from Northern California, Texas, and Alaska (Exhibits 6 and 7). These trends in soil PFAS concentrations may imply that when elevated concentrations are seen in soil, further investigation for local sources of PFAS use or handling may be warranted.

3.1.2 | Sediment

Four studies were identified reporting background concentrations for PFOS in sediment (Awad et al., 2011; Cochran, 2015; HPA, 2012; OECD, 2002), all of which were conducted in freshwater environments. As shown in Exhibit 3, detected dw PFOS concentrations ranged from 0.005 to 1.13 μg/kg dw from "multiple cities in the south and Midwest U.S." and the Niagara River. Detected ww PFOS concentrations ranged 0.18 to 2.2 μg/kg from one U.S. state and one Canadian province. One study was identified for PFOA in freshwater sediment (Awad et al., 2011). Two reported ww PFOA concentrations ranged from <0.05 to 0.1 μg/kg from three locations in one Canadian province.

EXHIBIT 3 Tabular summary of soil and sediment background studies

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Soil	Terrestrial	PFOA	Canada: Inuvick, NWT	μg/kg dw	–	0.118	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	Canada: Meanook, AB	μg/kg dw	–	0.059	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Ada, OK	μg/kg dw	–	0.464	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Auke Bay, AK	μg/kg dw	–	0.163	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Baton Rouge, LA	μg/kg dw	–	0.562	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Clearmont, WY	μg/kg dw	–	0.201	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Cleveland National Forest, CA	μg/kg dw	–	0.270	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Conyers, GA	μg/kg dw	–	1.770	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Cortland, NY	μg/kg dw	–	1.137	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Fertile, MN	μg/kg dw	–	0.132	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Fort Casey, WA	μg/kg dw	–	0.136	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Holderness, NH	μg/kg dw	–	1.248	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Houston, TX	μg/kg dw	–	–	–	–	2.66	Strynar et al., 2012
Soil	Terrestrial	PFOA	USA: Juneau, AK	μg/kg dw	–	0.989	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Kaibab National Forest, AZ	μg/kg dw	–	0.746	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Keystone, SD	μg/kg dw	–	0.210	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Laurel Fork, NC	μg/kg dw	–	–	–	–	1.35	Strynar et al., 2012
Soil	Terrestrial	PFOA	USA: Limon, CO	μg/kg dw	–	0.430	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Mt. Zion, CO	μg/kg dw	–	0.349	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Penns Grove, NJ	μg/kg dw	–	0.713	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Penns Grove, NJ	μg/kg dw	–	0.973	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Penns Grove, NJ	μg/kg dw	–	0.836	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Penns Grove, NJ	μg/kg dw	–	0.561	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Richmond, KY	μg/kg dw	–	–	–	–	2.14	Strynar et al., 2012
Soil	Terrestrial	PFOA	USA: RTP, NC	μg/kg dw	–	–	–	–	31.7	Strynar et al., 2012
Soil	Terrestrial	PFOA	USA: RTP, NC	μg/kg dw	–	–	–	–	15.6	Strynar et al., 2012
Soil	Terrestrial	PFOA	USA: Seward, NE	μg/kg dw	–	0.190	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Shandon, CA	μg/kg dw	–	0.094	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Shasta-Trinity National Forest, CA	μg/kg dw	–	1.838	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Shinning Rock, NC	μg/kg dw	–	–	–	–	8.4	Strynar et al., 2012
Soil	Terrestrial	PFOA	USA: St. Paul, MN	μg/kg dw	–	0.157	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: W. Layfayette, IN	μg/kg dw	–	–	–	–	2.18	Strynar et al., 2012
Soil	Terrestrial	PFOA	USA: Waimea, HI	μg/kg dw	–	0.112	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Whipple Dam State Park, PA	μg/kg dw	–	0.605	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA: Yellowstone National Park, WY	μg/kg dw	–	0.246	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA Commonwealth: El Yunque National Forest, PR	μg/kg dw	–	0.187	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA Commonwealth: El Yunque National Forest, PR	μg/kg dw	–	0.363	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOA	USA Commonwealth: Maraguez, PR	μg/kg dw	–	0.961	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	Canada: Inuvick, NWT	μg/kg dw	–	0.018	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	Canada: Meanook, AB	μg/kg dw	–	0.071	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Ada, OK	μg/kg dw	–	0.110	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Auke Bay, AK	μg/kg dw	–	0.030	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Baton Rouge, LA	μg/kg dw	–	0.700	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Clearmont, WY	μg/kg dw	–	0.226	–	–	–	Rankin et al., 2016

(*continued*)

EXHIBIT 3 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Soil	Terrestrial	PFOS	USA: Cleveland National Forest, CA	μg/kg dw	–	0.657	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Conyers, GA	μg/kg dw	–	1.956	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Cortland, NY	μg/kg dw	–	0.390	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Fertile, MN	μg/kg dw	–	0.112	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Fort Casey, WA	μg/kg dw	–	0.689	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Holderness, NH	μg/kg dw	–	1.809	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Houston, TX	μg/kg dw	–	–	–	–	2.16	Strynar et al., 2012
Soil	Terrestrial	PFOS	USA: Juneau, AK	μg/kg dw	–	1.145	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Kaibab National Forest, AZ	μg/kg dw	–	0.168	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Keystone, SD	μg/kg dw	–	0.182	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Laurel Fork, NC	μg/kg dw	–	–	–	–	2.52	Strynar et al., 2012
Soil	Terrestrial	PFOS	USA: Limon, CO	μg/kg dw	–	0.684	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Mt. Zion, CO	μg/kg dw	–	0.574	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Penns Grove, NJ	μg/kg dw	–	0.268	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Penns Grove, NJ	μg/kg dw	–	0.309	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Penns Grove, NJ	μg/kg dw	–	0.302	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Penns Grove, NJ	μg/kg dw	–	0.184	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Richmond, KY	μg/kg dw	–	–	–	–	1.6	Strynar et al., 2012
Soil	Terrestrial	PFOS	USA: RTP, NC	μg/kg dw	–	–	–	–	2.55	Strynar et al., 2012
Soil	Terrestrial	PFOS	USA: RTP, NC	μg/kg dw	–	–	–	–	0.606	Strynar et al., 2012
Soil	Terrestrial	PFOS	USA: Seward, NE	μg/kg dw	–	0.326	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Shandon, CA	μg/kg dw	–	0.109	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Shasta-Trinity National Forest, CA	μg/kg dw	–	0.063	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Shinning Rock, NC	μg/kg dw	–	–	–	–	1.47	Strynar et al., 2012
Soil	Terrestrial	PFOS	USA: St. Paul, MN	μg/kg dw	–	0.303	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: W. Layfayette, IN	μg/kg dw	–	–	–	–	<0.5	Strynar et al., 2012
Soil	Terrestrial	PFOS	USA: Waimea, HI	μg/kg dw	–	0.035	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Whipple Dam State Park, PA	μg/kg dw	–	0.561	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA: Yellowstone National Park, WY	μg/kg dw	–	0.148	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA Commonwealth: El Yunque National Forest, PR	μg/kg dw	–	0.149	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA Commonwealth: El Yunque National Forest, PR	μg/kg dw	–	0.350	–	–	–	Rankin et al., 2016
Soil	Terrestrial	PFOS	USA Commonwealth: Maraguez, PR	μg/kg dw	–	0.158	–	–	–	Rankin et al., 2016
Sediment	Freshwater	PFOA	Canada: Toronto, ON	μg/kg ww	–	–	–	<0.05	0.2	Awad et al., 2011
Sediment	Freshwater	PFOS	Canada: Toronto, ON	μg/kg ww	–	–	–	<0.1	2.2	Awad et al., 2011
Sediment	Freshwater	PFOS	USA: Decatur, AL	μg/kg ww	–	–	–	0.18	0.98	OECD, 2002
Sediment	Freshwater	PFOS	USA: Bossier City, LA	μg/kg dw	–	–	–	0	0	Cochran, 2015
Sediment	Freshwater	PFOS	USA: multiple cities in the south and midwest	μg/kg dw	–	–	–	N/A	1.13	OECD, 2002
Sediment	Freshwater	PFOS	USA/Canada: Niagara River, NY	μg/kg dw	–	–	–	0.005	1.1	HPA, 2012

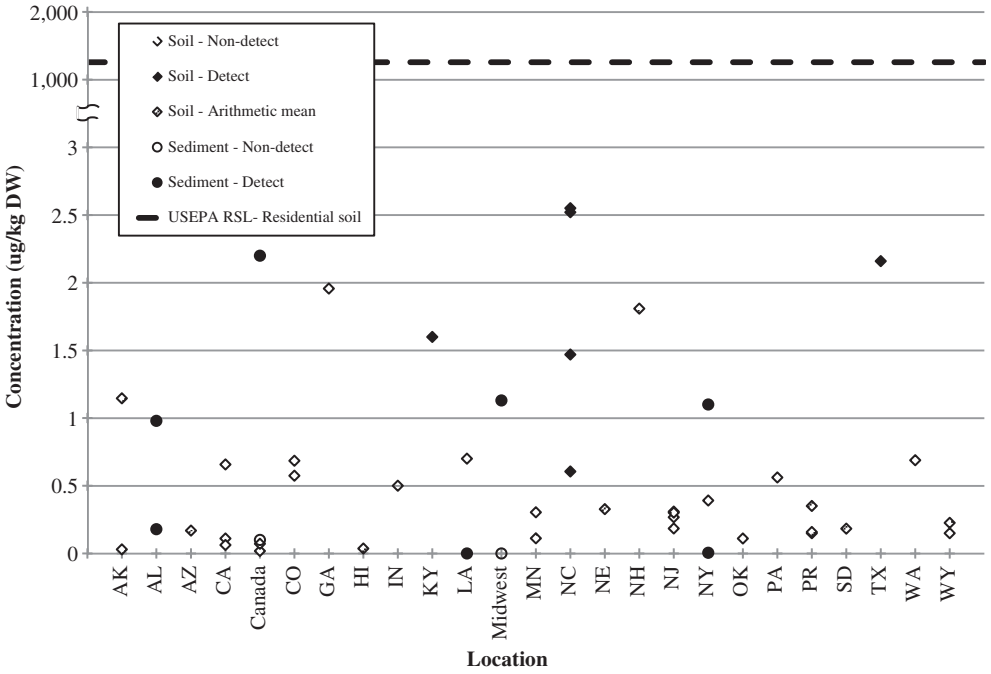


EXHIBIT 4 Number of background data points for abiotic media

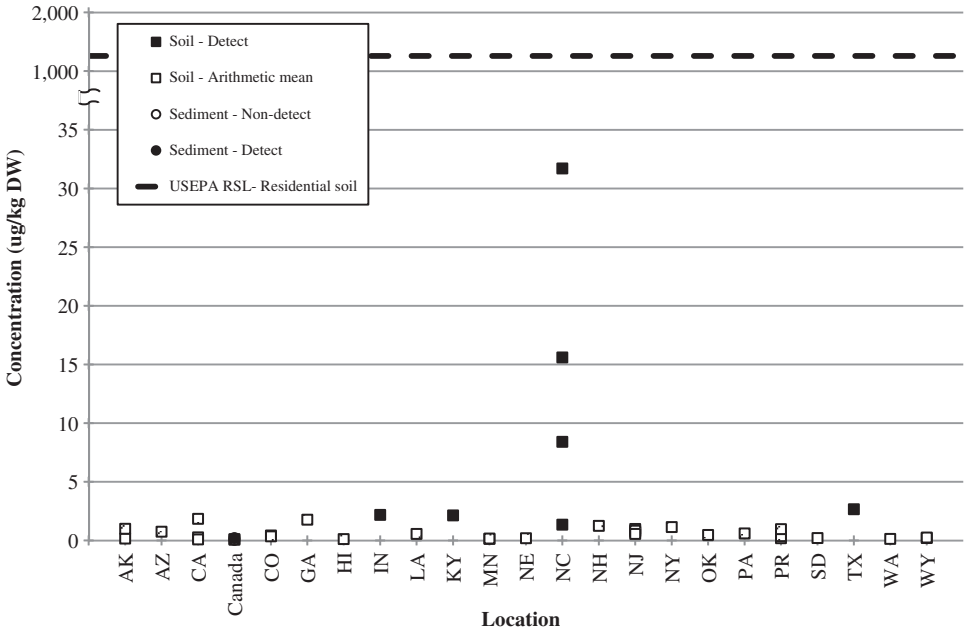


EXHIBIT 5 Scatter plot of soil and sediment background data for PFOS

Only minimum and maximum concentrations were reported in these studies.

Currently, there are no sediment screening levels protective of human health, therefore, the residential soil RSL was used to compare to the sediment results for PFOS and PFOA. All background sediment concentrations are well below the soil RSL, by two to three orders of magnitude (Exhibits 4 and 5).

The range of the sediment background data for PFOS is wider than the range demonstrated for soil, with approximately two to three orders of magnitude difference between the minimum and maximum detections of PFOS in sediment. Too few sediment data points were identified for PFOA to conduct this kind of assessment. Since sediments may reflect PFAS inputs from overland sources as well as from the local aquatic system, the evaluation of sediments at PFAS-contaminated sites should include characterization of upstream sediments and surface waters.

3.1.3 | Surface water

Exhibit 8 presents a summary of the background data reported for surface water, Exhibits 9 and 10 display the surface water data on a scatter plot, and Exhibits 11 and 12 illustrate the data as geographically

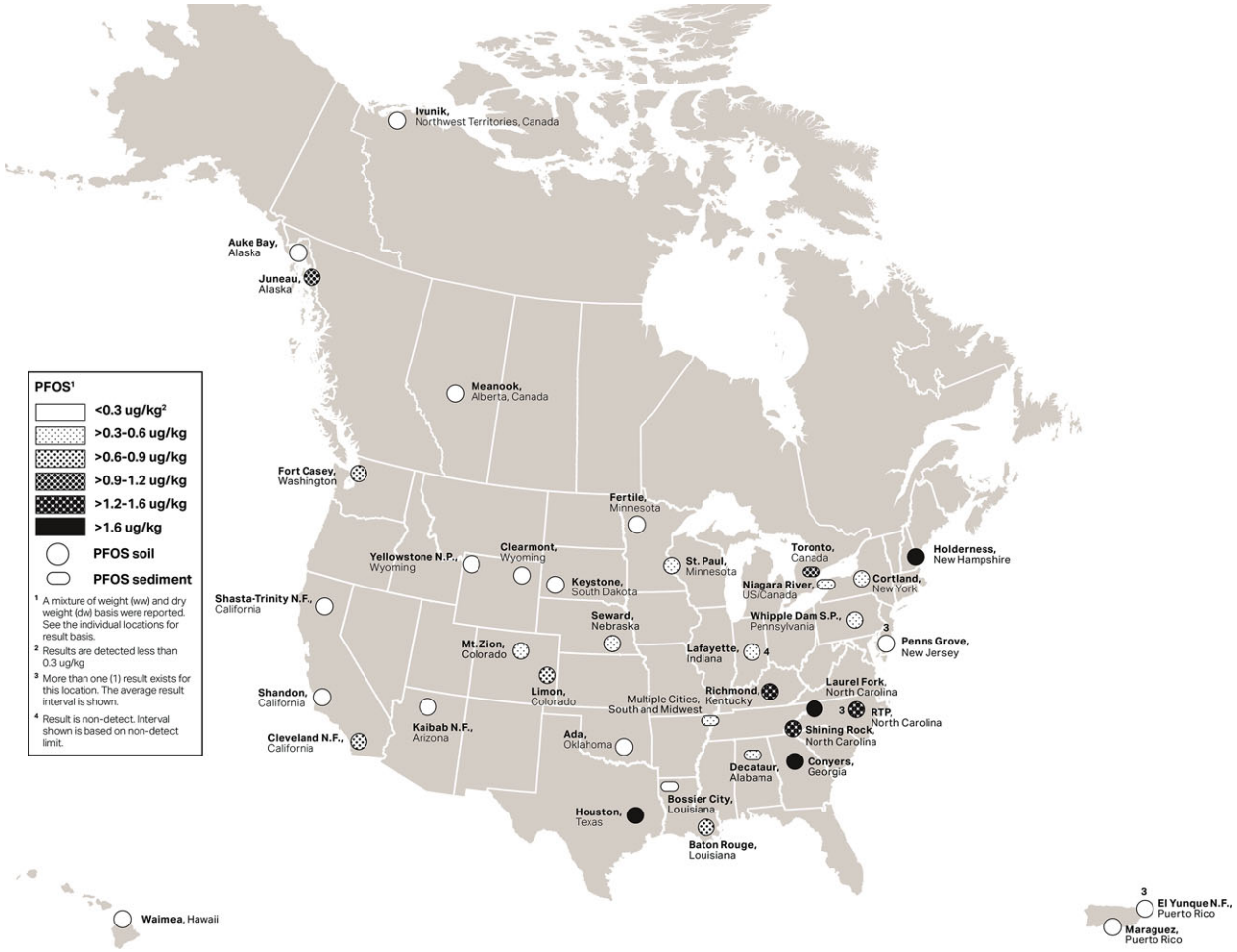


EXHIBIT 6 Scatter plot of soil and sediment background data for PFOA

specific concentration ranges presented on a map of the United States and Canada.

As shown in Exhibit 8, 15 studies were identified for PFOS in surface water of freshwater environments (Awad et al., 2011; Boulanger, Vargo, Schnoor, & Hornbuckle, 2004; De Silva, Spencer, Scott, Backus, & Muir, 2011; Hansen, Johnson, Eldridge, Butenhoff, & Dick, 2002; Kannan et al., 2005; Kim & Kannan, 2007; Konwick et al., 2008; Lanza, 2015; Moody, Martin, Kwan, Muir, & Mabury, 2002; Nakyayama et al., 2007; OECD, 2002; Plumlee, Larabee, & Reinhard, 2008; Simcik & Dorweiler, 2005; Sinclair, Mayack, Roblee, Yamashita, & Kannan, 2006; Sinclair, Taniyasu, Yamashita, & Kannan, 2004). Thirty-three results with detected concentrations ranged from 0.8 to 2,930 ng/L for eight U.S. states, five of the Great Lakes, and one province in Canada. Arithmetic and geometric mean concentrations of PFOS ranged from 0.26 to 46 ng/L. One paper (OECD, 2002), from which the maximum detected concentration of 2,930 ng/L (maximum reported for "quiet freshwater") was extracted, reported the range in concentration from six cities, of which, only two were control cities that did not report significant fluorochemical activities (Cleveland, Ohio, and Port St. Lucie, Florida). Due to this uncertainty and the fact that the authors stated that the control cities generally inhabited the lower end of the ranges, the maximum concentration of 2,930 ng/L was believed to be from a known impacted city and therefore discarded as a background sample. The remaining range for PFOS in background freshwater bodies was 0.8 to 138 ng/L (maximum reported for "surface water"). The results reported were a mixture of arithmetic means and detected concentration ranges. The maximum concentration would exceed risk-based advisories if untreated surface water were used for potable purposes.

These same 14 studies listed earlier for PFOS, with the exception of OECD (2002) and including one study that only reported PFOA data (DuPont, 2008), also identified PFOA background concentrations in freshwater environments. Thirty-two results exhibited detected concentrations ranging from 0.45 to 287 ng/L for eight U.S. states, the five Great Lakes, and one Canadian province. Arithmetic and geometric mean concentrations of PFOA ranged from 0.65 to 43.4 ng/L.

Three studies were identified that contained background marine and estuarine surface water (Konwick et al., 2008; Umweltbundesamt, 2009; Yamashita et al., 2005). Detected concentrations of PFOS ranged from 0.0011 to 2.9 ng/L and detected PFOA concentrations ranged from 0.015 to 3.7 ng/L. Minimum and maximum concentrations were reported from one U.S. state (Georgia) and the Atlantic and Pacific Oceans.

The variation in the freshwater background data for PFOS and PFOA falls within approximately two to three orders of magnitude difference between the minimum and maximum detections, and one to two orders of magnitude difference between the highest and lowest

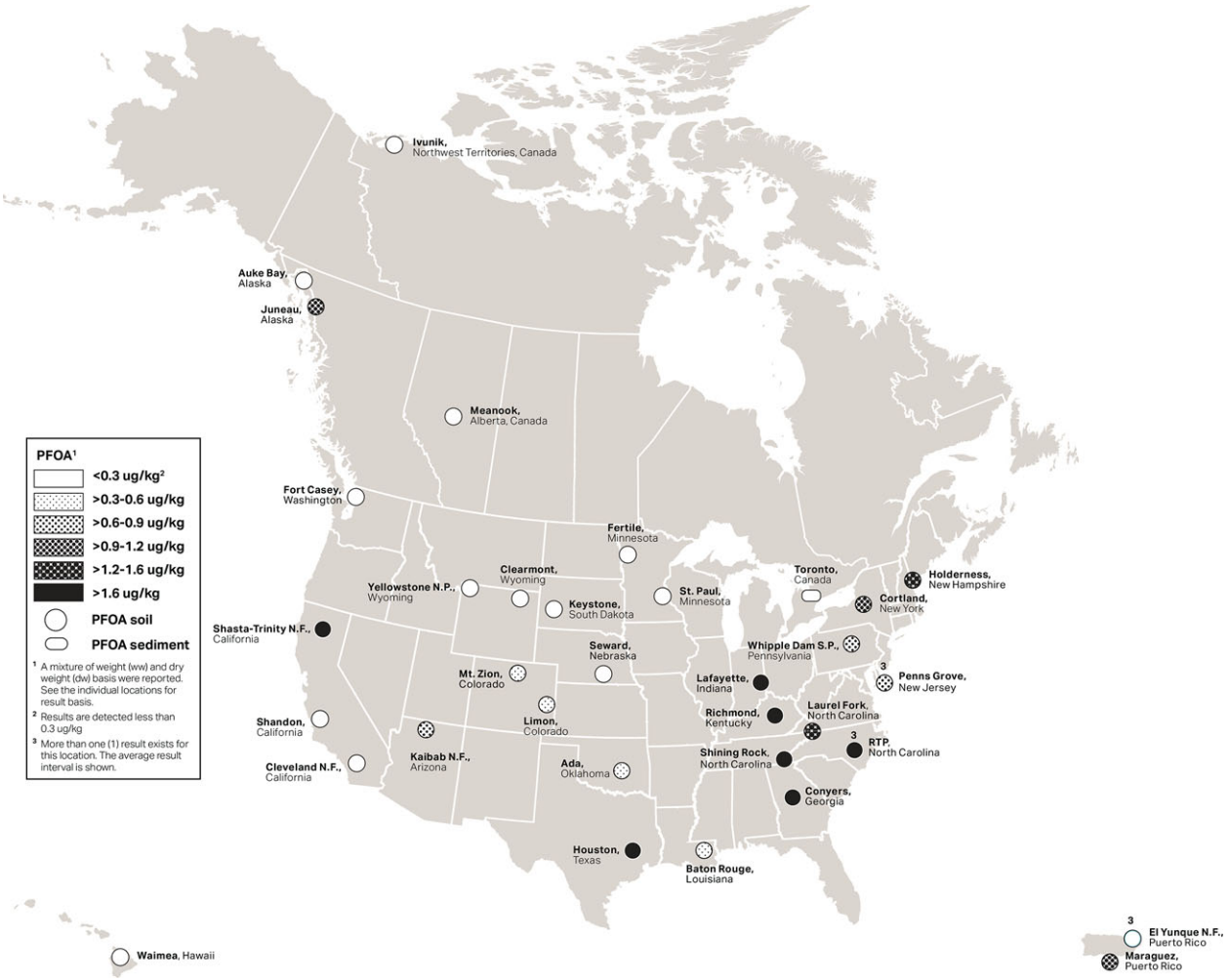


EXHIBIT 7 Locations in the United States and Canada with soil and sediment background data for PFOS

mean concentrations (Exhibits 9 and 10). A similar spread in the data was also demonstrated for the few individual marine and estuarine water samples. If the freshwater bodies cited were used as a drinking water source, maximum concentrations of PFOS and PFOA would exceed the drinking water health advisories (USEPA, 2016a, 2016b) (i.e., 70 ng/L), while arithmetic and geometric mean concentrations fall below this advisory level.

Studies on freshwater bodies from the Great Lakes Region comprise the majority of surface water samples, with some deep water samples collected from the Pacific and Atlantic Oceans (Exhibits 11 and 12). In general, PFOS and PFOA concentrations in the marine samples are much lower than concentrations detected in freshwater samples.

3.1.4 | Drinking water

Exhibit 13 presents a summary of the data reported for drinking water, Exhibits 14 and 15 display the drinking water data on scatter plots, and Exhibits 16 and 17 illustrate the data as geographically specific concentration ranges presented on a map of North America.

One study was identified that contained drinking water results (USEPA, 2016d), which reported national drinking water PFAS concentrations from USEPA's UCMR3 requiring public water systems to monitor for these constituents.

As shown in Exhibit 13, 54 geometric means for PFOS ranged from <40 to 43 ng/L and PFOA ranged from <20 to 22 ng/L. Individual data results for PFOS ranged from <40 to 1,800 ng/L and PFOA ranged from <20 to 349 ng/L. Results were reported from 50 U.S. states, two U.S. territories, U.S. District of Columbia, and one U.S. Native American Nation.

The range of values in the drinking water data for PFOS and PFOA is narrow, based on the geometric mean concentrations reported for each geographic location, although there is a wider spread in the individual data points for this medium which can differ by approximately one to two orders of magnitude (Exhibits 14 and 15). Both PFOS and PFOA demonstrate geometric mean concentrations similar to their respective detection limits (40 ng/L for PFOS and 20 ng/L for PFOA). While individual sample exceedences occur, geometric mean concentrations for both PFOS and PFOA do not exceed the drinking water health advisory (70 ng/L).

This dataset indicates that the highest levels of PFAS have been detected in public water systems in the Northeast United States, Colorado, and Minnesota (Exhibits 16 and 17), which is similar to findings in another recent study that evaluated in the UCMR3 data (Hu et al., 2016). Because Hu et al. (2016) processed the UCMR3 data differently

EXHIBIT 8 Tabular summary of surface water background studies: freshwater and saltwater

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Surface water	Freshwater	PFOA	Canada: Toronto, ON	ng/L	–	–	–	4.7	44	Awad et al., 2011
Surface water	Freshwater	PFOA	Canada: Toronto, ON	ng/L	11	–	–	<0.25	33	Moody et al., 2002
Surface water	Freshwater	PFOA	USA: Albany, NY	ng/L	–	8.61	7.2	3.27	15.8	Kim & Kannan, 2007
Surface water	Freshwater	PFOA	USA: Cape Fear Basin, NC	ng/L	–	43.4	12.6	<0.05	287	Nakyayama et al., 2007
Surface water	Freshwater	PFOA	USA: Conasauga River, GA	ng/L	–	32.8	–	21.5	47	Konwick et al., 2008
Surface water	Freshwater	PFOA	USA: Decatur, AL	ng/L	–	<25	–	–	<25	Hansen et al., 2002
Surface water	Freshwater	PFOA	USA: Bossier City, LA	ng/L	–	–	–	0	0	Cochran, 2015
Surface water	Freshwater	PFOA	USA: Erie Canal, NY	ng/L	–	–	30	25	59	Sinclair et al., 2006
Surface water	Freshwater	PFOA	USA: Finger Lakes, NY	ng/L	–	–	14	11	20	Sinclair et al., 2006
Surface water	Freshwater	PFOA	USA: Hudson River, NY	ng/L	–	–	35	22	173	Sinclair et al., 2006
Surface water	Freshwater	PFOA	USA: Lake Champlain, NY	ng/L	–	–	24	10	46	Sinclair et al., 2006
Surface water	Freshwater	PFOA	USA: Lake Erie	ng/L	–	5.46	–	–	–	De Silva et al., 2011
Surface water	Freshwater	PFOA	USA: Lake Erie	ng/L	35	–	–	21	47	Boulanger et al., 2004
Surface water	Freshwater	PFOA	USA: Lake Erie	ng/L	–	–	15	13	27	Sinclair et al., 2006
Surface water	Freshwater	PFOA	USA: Lake Huron	ng/L	–	3.22	–	–	–	De Silva et al., 2011
Surface water	Freshwater	PFOA	USA: Lake Michigan	ng/L	–	4.1	–	–	–	De Silva et al., 2011
Surface water	Freshwater	PFOA	USA: Lake Michigan	ng/L	–	–	–	<0.28	3.37	Simcik & Dorweiler, 2005
Surface water	Freshwater	PFOA	USA: Lake Oneida, NY	ng/L	–	–	19	19	19	Sinclair et al., 2006
Surface water	Freshwater	PFOA	USA: Lake Ontario	ng/L	–	4.31	–	–	–	De Silva et al., 2011
Surface water	Freshwater	PFOA	USA: Lake Ontario	ng/L	42	–	–	15	70	Boulanger et al., 2004
Surface water	Freshwater	PFOA	USA: Lake Ontario	ng/L	–	–	21	18	34	Sinclair et al., 2006
Surface water	Freshwater	PFOA	USA: Lake Superior	ng/L	–	0.65	–	–	–	De Silva et al., 2011
Surface water	Freshwater	PFOA	USA: MI	ng/L	–	–	–	<8	16	Sinclair et al., 2004
Surface water	Freshwater	PFOA	USA: MN	ng/L	–	–	–	<0.14	0.66	Simcik & Dorweiler, 2005
Surface water	Freshwater	PFOA	USA: MN	ng/L	–	–	–	0.45	19.4	Simcik & Dorweiler, 2005
Surface water	Freshwater	PFOA	USA: Niagara River, NY	ng/L	–	–	19	18	22	Sinclair et al., 2006
Surface water	Freshwater	PFOA	USA: Raisin River, MI	ng/L	–	–	–	14.7	14.7	Kannan et al., 2005

(*continued*)

EXHIBIT 8 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Surface water	Freshwater	PFOA	USA: San Jose, CA	ng/L	–	–	–	10	36	Plumlee et al., 2008
Surface water	Freshwater	PFOA	USA: San Jose, CA	ng/L	–	–	–	N/A	13	Plumlee et al., 2008
Surface water	Freshwater	PFOA	USA: St. Clair River, MI	ng/L	–	4.4	–	4	5	Kannan et al., 2005
Surface water	Freshwater	PFOA	USA: WV	ng/L	<50	–	–	–	–	DuPont, 2008
Surface water	Freshwater	PFOS	Canada: Toronto, ON	ng/L	–	–	–	3.1	37	Awad et al., 2011
Surface water	Freshwater	PFOS	Canada: Toronto, ON	ng/L	<10	–	–	<10	<10	Moody et al., 2002
Surface water	Freshwater	PFOS	USA: Albany, NY	ng/L	–	4.14	2.88	<0.25	9.3	Kim & Kannan, 2007
Surface water	Freshwater	PFOS	USA: Cape Fear Basin, NC	ng/L	–	31.2	28.9	<1	132	Nakyayama et al., 2007
Surface water	Freshwater	PFOS	USA: Conasauga River, GA	ng/L	–	6	–	2.3	12.8	Konwick et al., 2008
Surface water	Freshwater	PFOS	USA: Decatur, AL	ng/L	–	–	–	9	53	OECD, 2002
Surface water	Freshwater	PFOS	USA: Decatur, AL	ng/L	–	32	32.17	16.8	54.1	Hansen et al., 2002
Surface water	Freshwater	PFOS	USA: Bossier City, LA	ng/L	–	–	–	10	10	Cochran, 2015
Surface water	Freshwater	PFOS	USA: Erie Canal, NY	ng/L	–	–	6.4	5.7	13	Sinclair et al., 2006
Surface water	Freshwater	PFOS	USA: Finger Lakes, NY	ng/L	–	–	1.6	1.3	2.6	Sinclair et al., 2006
Surface water	Freshwater	PFOS	USA: Hudson River, NY	ng/L	–	–	1.7	1.5	3.4	Sinclair et al., 2006
Surface water	Freshwater	PFOS	USA: Lake Champlain, NY	ng/L	–	–	2.7	0.8	7.7	Sinclair et al., 2006
Surface water	Freshwater	PFOS	USA: Lake Erie	ng/L	30	–	–	11	39	Boulanger et al., 2004
Surface water	Freshwater	PFOS	USA: Lake Erie	ng/L	–	2.84	–	–	–	De Silva et al., 2011
Surface water	Freshwater	PFOS	USA: Lake Erie	ng/L	–	–	3	2.8	5.5	Sinclair et al., 2006
Surface water	Freshwater	PFOS	USA: Lake Huron	ng/L	–	2.25	–	–	–	De Silva et al., 2011
Surface water	Freshwater	PFOS	USA: Lake Michigan	ng/L	–	–	–	0.93	3.12	Simcik & Dorweiler, 2005
Surface water	Freshwater	PFOS	USA: Lake Michigan	ng/L	–	2	–	–	–	De Silva et al., 2011
Surface water	Freshwater	PFOS	USA: Lake Oneida, NY	ng/L	–	–	3.5	3.5	3.5	Sinclair et al., 2006
Surface water	Freshwater	PFOS	USA: Lake Ontario	ng/L	46	–	–	15	121	Boulanger et al., 2004
Surface water	Freshwater	PFOS	USA: Lake Ontario	ng/L	–	5.51	–	–	–	De Silva et al., 2011
Surface water	Freshwater	PFOS	USA: Lake Ontario	ng/L	–	–	4.9	2.9	30	Sinclair et al., 2006
Surface water	Freshwater	PFOS	USA: Lake Superior	ng/L	–	0.26	–	–	–	De Silva et al., 2011

(*continued*)

EXHIBIT 8 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Surface water	Freshwater	PFOS	USA: MI	ng/L	–	–	–	2	5	Sinclair et al., 2004
Surface water	Freshwater	PFOS	USA: MN	ng/L	–	–	–	<0.23	1.23	Simcik & Dorweiler, 2005
Surface water	Freshwater	PFOS	USA: MN	ng/L	–	–	–	2.38	46.57	Simcik & Dorweiler, 2005
Surface water	Freshwater	PFOS	USA: multiple cities in the south and midwest	ng/L	–	–	–	N/A	138	OECD, 2002
Surface water	Freshwater	PFOS	USA: multiple cities in the south and midwest	ng/L	–	–	–	N/A	2,930	OECD, 2002
Surface water	Freshwater	PFOS	USA: Niagara River, NY	ng/L	–	–	5.5	3.3	6.7	Sinclair et al., 2006
Surface water	Freshwater	PFOS	USA: Raisin River, MI	ng/L	–	–	–	3.5	3.5	Kannan et al., 2005
Surface water	Freshwater	PFOS	USA: San Jose, CA	ng/L	–	–	–	27	56	Plumlee et al., 2008
Surface water	Freshwater	PFOS	USA: San Jose, CA	ng/L	–	–	–	4.8	25	Plumlee et al., 2008
Surface water	Freshwater	PFOS	USA: St. Clair River, MI	ng/L	–	2.6	–	1.9	3.9	Kannan et al., 2005
Surface water	Estuarine	PFOA	USA: Altamaha River, GA	ng/L	–	3.0 - 3.1	–	2.6	3.7	Konwick et al., 2008
Surface water	Estuarine	PFOS	USA: Altamaha River, GA	ng/L	–	2.6 - 2.7	–	2.3	2.9	Konwick et al., 2008
Surface water	Marine	PFOA	Central to Eastern Pacific	ng/L	–	–	–	0.015	0.062	Yamashita et al., 2005
Surface water	Marine	PFOA	Central to Eastern Pacific Ocean (4K-4.4 Km)	ng/L	–	–	–	0.045	0.056	Yamashita et al., 2005
Surface water	Marine	PFOA	Mid Atlantic	ng/L	–	–	–	0.1	0.439	Yamashita et al., 2005
Surface water	Marine	PFOA	North Atlantic	ng/L	–	–	–	0.16	0.338	Yamashita et al., 2005
Surface water	Marine	PFOA	North Atlantic, Arctic	ng/L	–	–	–	0.04	0.1	Umweltbundesamt, 2009
Surface water	Marine	PFOS	Central to Eastern Pacific	ng/L	–	–	–	0.0011	0.02	Yamashita et al., 2005
Surface water	Marine	PFOS	Central to Eastern Pacific Ocean (4K-4.4 Km)	ng/L	–	–	–	0.0032	0.0034	Yamashita et al., 2005
Surface water	Marine	PFOS	Mid Atlantic	ng/L	–	–	–	0.037	0.073	Yamashita et al., 2005
Surface water	Marine	PFOS	North Atlantic	ng/L	–	–	–	0.0086	0.036	Yamashita et al., 2005
Surface water	Marine	PFOS	North Atlantic, Arctic	ng/L	–	–	–	0.01	0.05	Umweltbundesamt, 2009

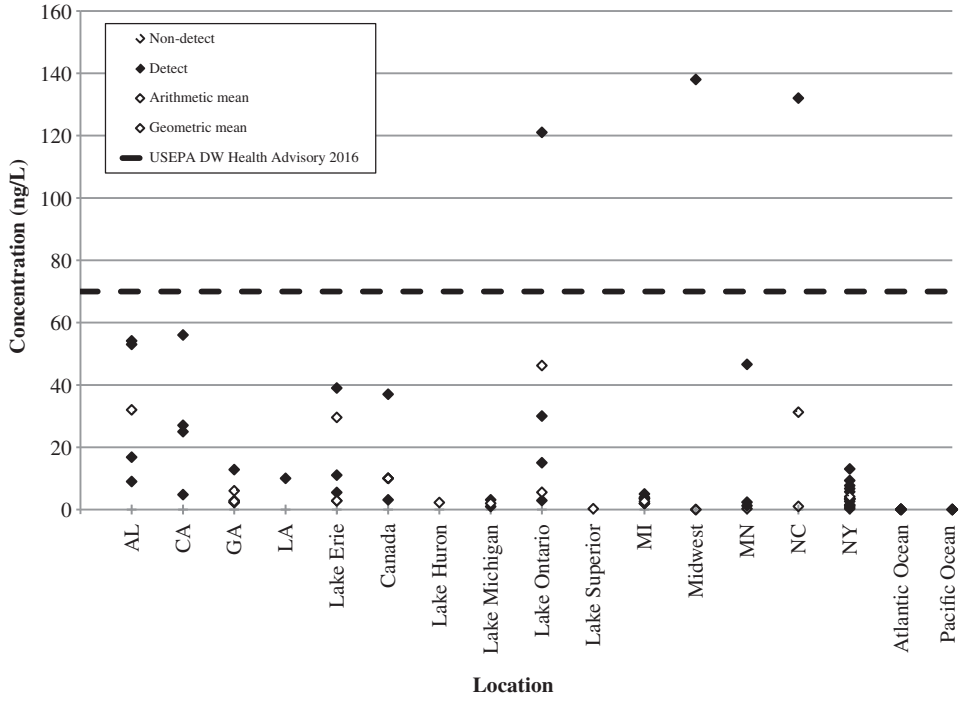


EXHIBIT 9 Locations in the United States and Canada with soil and sediment background data for PFOA

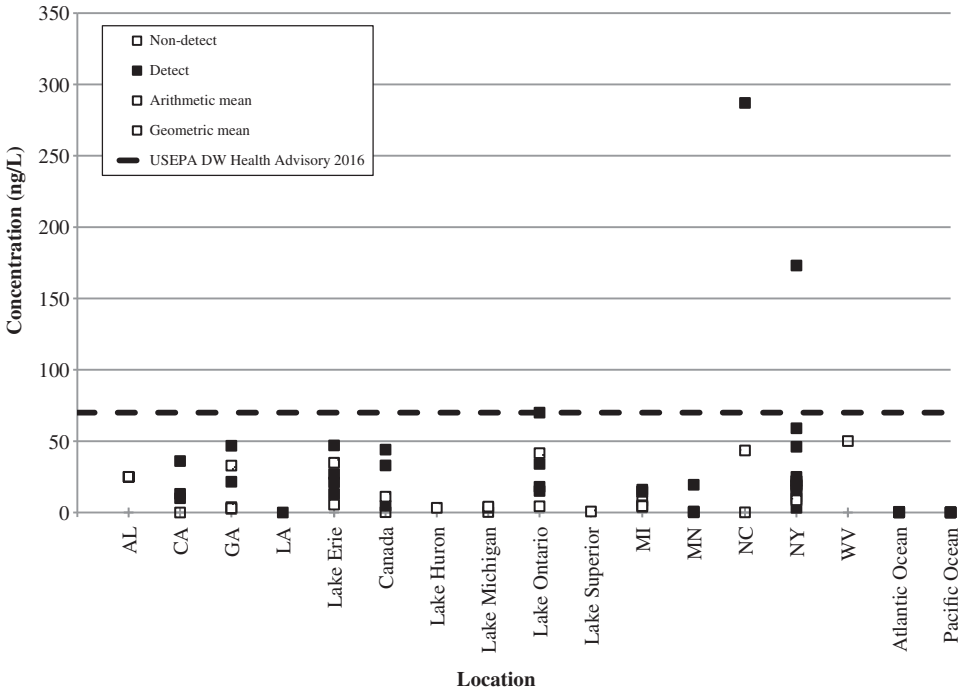


EXHIBIT 10 Scatter plot of surface water background data for PFOS: freshwater and saltwater

than in the current study, in which the geometric mean for each state was calculated thus mitigating bias from extreme values, a few additional states with elevated concentrations of PFOS and PFOA were identified in Hu et al. (2016). In the context of contaminated sites, these data illustrate the importance of a well-defined conceptual site model for groundwater and surface water flows and understanding PFAS levels in upgradient locations.

3.2 | Biotic media

The biotic media of interest were limited to human blood (i.e., whole blood, blood serum, umbilical cord blood, and plasma) and fish and shellfish tissue, but other available media included human liver, human breast milk, birds, mammals, produce, milk, and meat.

Exhibit 18 presents a summary of the background data reported for human blood, Exhibits 19 and 20 display the serum data on scatter

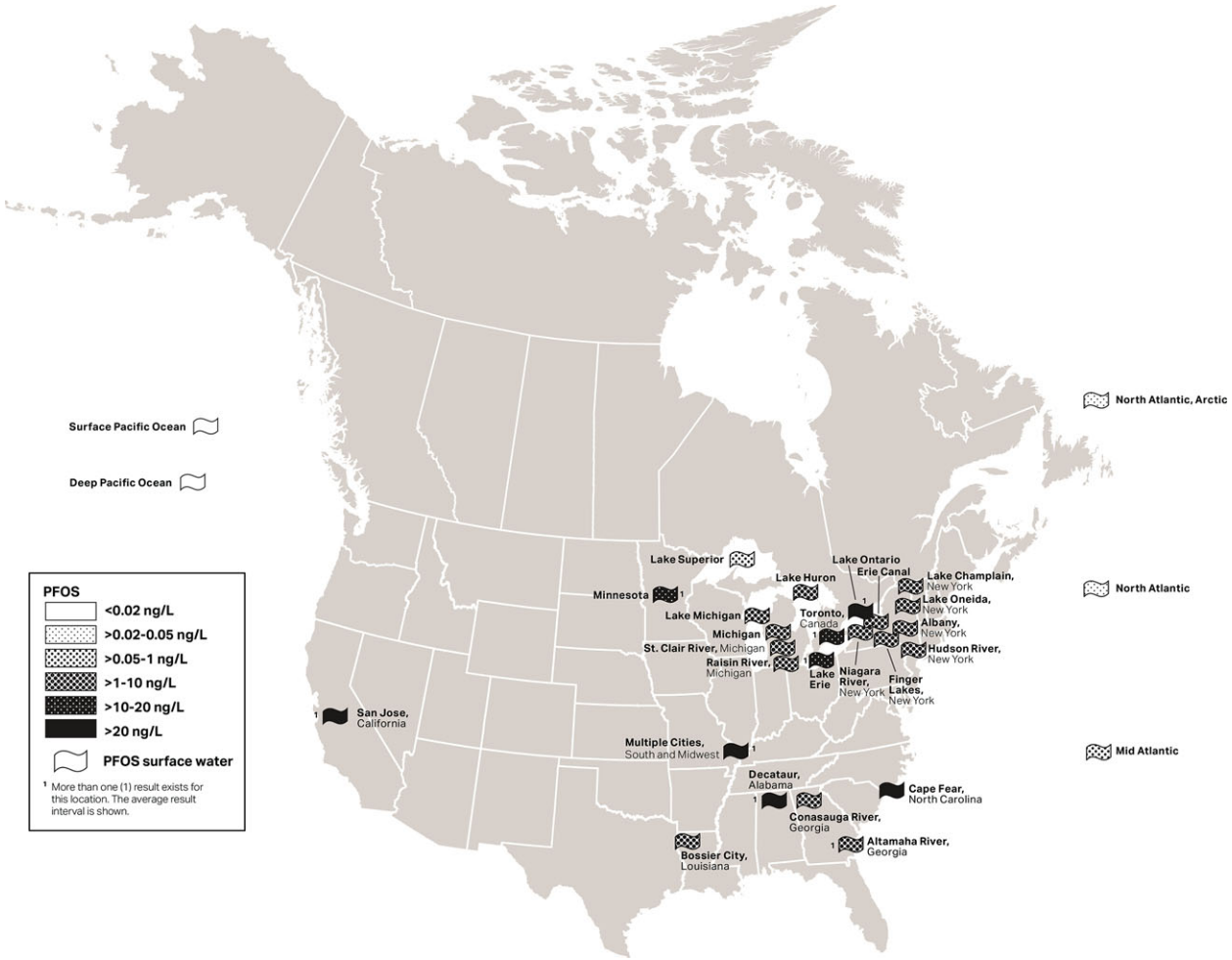


EXHIBIT 11 Scatter plot of surface water background data for PFOA: freshwater and saltwater

plots, and Exhibits 21 and 22 illustrate the human blood data as geographically specific concentration ranges presented on a map of North America.

3.2.1 | Whole blood

As shown in Exhibit 18, one study was identified (Kannan et al., 2004) that contained whole blood results for humans, and only PFOA was reported. Arithmetic mean PFOA concentrations ranged from 23 to 66 ng/mL and individual data points with detections ranged from 11 to 164 ng/mL. Male and female results were reported separately and only the mean, minimum, and maximum concentrations were reported from a total of 30 samples from one U.S. state (Kentucky). No trends were noted due to the small sample size.

3.2.2 | Blood serum

Twenty-six studies were identified (Apelberg et al., 2007; ATSDR, 2015; Beesoon et al., 2011; Biomonitoring California, 2015a, 2015b; Calafat, Kuklenyik, Caudill, Reidy, & Needham, 2006a; Calafat et al., 2006b; CDC, 2017; D'eon, Crozier, Furdui, Reiner, & Mabury, 2009; De Silva & Mabury, 2006; Hamm, Cherry, Chan, Martin, & Burstyn, 2010; Hansen, Clemen, Ellefson, & Johnson, 2001; Kannan, Kumar, Corsolini, & Aldous, 2003; Kato et al., 2009; Kubwabo, Vais, & Benoit, 2004; Kuklenyik, Reich, Tully, Needham, & Calafat, 2004; Monroy et al., 2008; New York State Department of Health [NYSDOH], 2016; OECD, 2002; Olsen et al., 2003a; Olsen, Hansen, Stevenson, Burris, & Mandel, 2003b; Olsen et al., 2004a, 2004b, 2007; Tittlemier, Ryan, & Oostdam, 2004; ToxConsultant, 2014) that contained background human blood serum concentrations. Results with unknown locations or wide-ranging locations (e.g., U.S. blood banks) were reviewed but not included in ranges. The dataset for blood serum contained a mixture of arithmetic and geometric mean concentrations, and most studies did not provide both of these statistics. Therefore, reference to mean concentrations in blood serum reflects a mixture of arithmetic and geometric mean concentrations from various studies.

As shown in Exhibit 18, 19 mean concentrations of PFOS ranged from 2.55 to 55.8 ng/mL in nine U.S. states, four Canadian provinces, and several unspecified locations in the United States and Canada. Individual data points with detections ranged from 3.6 to 1,656 ng/mL. The maximum detected concentration was from a study in Portland, Oregon (Olsen et al., 2003a), which may be an anomaly in the dataset (not related to background) as the next highest concentration is 515 ng/mL and is more in line with the remaining upper-end data points. Due to the fact that the majority of reported results came from blood banks and only demographic information was obtained, the maximum

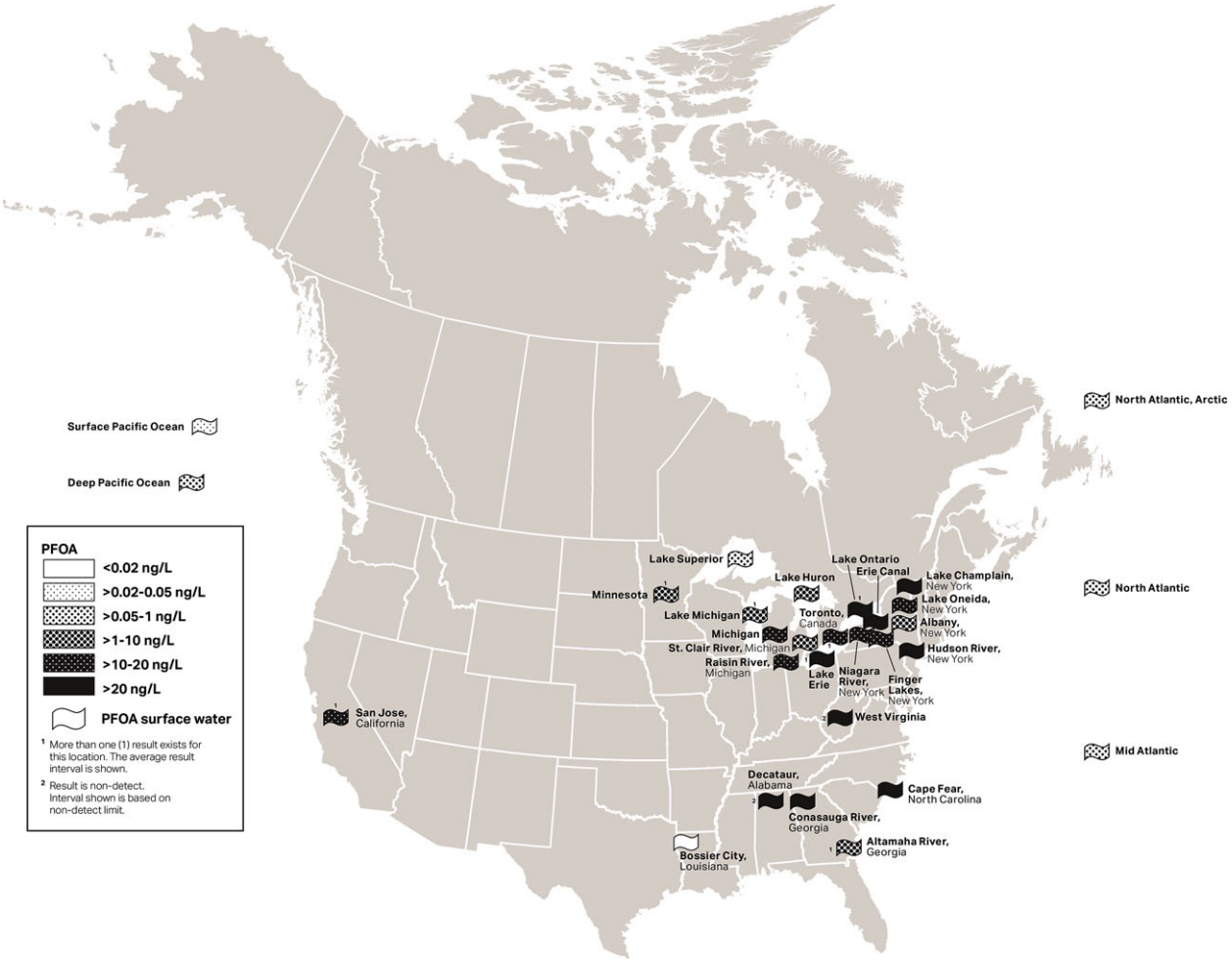


EXHIBIT 12 Locations in the United States and Canada with surface water background data for PFOS

concentration of 1,656 ng/mL (approximate average serum concentration of a PFOS-related production worker) was not included in the range of individual data points listed earlier. The spread in the blood serum data for PFOS is relatively narrow, based on the mean concentrations reported for each location, with a much wider spread in the individual data points for this medium which can differ by between two and three orders of magnitude (Exhibit 19). Geometric and arithmetic mean concentrations of PFOS for several states exceed the CDC's general population blood serum level of 21.7 ng/mL (ATSDR, 2017), which is reported to represent 95 percent of the general population of the United States. However, even the upper end of the mean concentrations of 57.97 ng/mL is less than three times higher than the CDC's level, and most of the means hover around this level. Several individual data points for PFOS are well above the CDC's level.

Mean concentrations of PFOA ranged from 0.47 to 23.5 ng/mL in 11 U.S. states and two Canadian provinces. Individual data points with detections range from 0.2 to77.2 ng/mL. All but two Canadian locations reported both mean and minimum/maximum results. The spread in the blood serum data for PFOA is even tighter than the data for PFOS based on the mean concentrations, with a wider spread in the individual data points which can differ between two and three orders of magnitude (Exhibit 20). Most geometric and arithmetic mean concentrations of PFOA are less than or equivalent to the CDC's general population 95th percentile blood serum level of 5.7 ng/mL (ATSDR, 2017). The upper end of the mean concentrations of 23.5 ng/mL is approximately four times higher than the CDC's level, and several individual data points for PFOS are above the CDC's level.

Fewer trends are noted for PFOS and PFOA in blood serum data collected from the United States and Canada than are noted for drinking water and soil, although higher overall serum levels are reported for the United States in the northeastern and southeastern states (Exhibits 21 and 22). Certain west coast cities, such as Seattle and Los Angeles, and even northern Canada also exhibit moderate PFOS levels (30 ng/mL to 50 ng/mL). Very few blood serum studies have been conducted in the central United States, and little can be said about patterns in serum concentrations in this region.

3.2.3 | Umbilical cord blood

Four studies were identified (Apelberg et al., 2007; Beesoon et al., 2011; Monroy et al., 2008; Tittlemier et al., 2004) that contained human umbilical cord blood results from two Canadian provinces and one U.S. state (Maryland) (Exhibit 18). Mean concentrations of PFOS

EXHIBIT 13 Tabular summary of drinking water background studies

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Drinking water	N/A	PFOA	USA: Alabama	ng/L	20.2	–	–	<20	100	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Alaska	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Arizona	ng/L	20.2	–	–	<20	50	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Arkansas	ng/L	20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: California	ng/L	20.0	–	–	<20	53	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Colorado	ng/L	21.5	–	–	<20	90	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Connecticut	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Delaware	ng/L	21.7	–	–	<20	140	USEPA, 2016d
Drinking water	N/A	PFOA	USA: District of Columbia (DC)	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Florida	ng/L	20.0	–	–	<20	65	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Georgia	ng/L	20.2	–	–	<20	70	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Hawaii	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Idaho	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Illinois	ng/L	20.0	–	–	<20	59	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Indiana	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Iowa	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Kansas	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	NA	PFOA	USA: Kentucky	ng/L	20	–	–	<20	20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Louisiana	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Maine	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Maryland	ng/L	20.0	–	–	<20	21.23	USEPA, 2016d
Drinking water	NA	PFOA	USA: Massachusetts	ng/L	20.1	–	–	<20	62	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Michigan	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Minnesota	ng/L	20.6	–	–	<20	338	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Mississippi	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Missouri	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Montana	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Nebraska	ng/L	<20	–	–	<20	<20	USEPA, 2016d

(*continued*)

EXHIBIT 13 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Drinking water	N/A	PFOA	USA: Nevada	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: New Hampshire	ng/L	20.4	–	–	<20	67	USEPA, 2016d
Drinking water	N/A	PFOA	USA: New Jersey	ng/L	20.4	–	–	<20	110	USEPA, 2016d
Drinking water	N/A	PFOA	USA: New Mexico	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: New York	ng/L	20.0	–	–	<20	48	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Navajo Nation	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: North Carolina	ng/L	20.0	–	–	<20	30	USEPA, 2016d
Drinking water	N/A	PFOA	USA: North Dakota	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Ohio	ng/L	20.0	–	–	<20	27	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Oklahoma	ng/L	20.0	–	–	<20	40	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Oregon	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Pennsylvania	ng/L	20.4	–	–	<20	349	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Region 1: Tribal	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Region 10: Tribal	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Region 5: Tribal	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Region 6: Tribal	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Region 8: Tribal	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Region 9: Tribal	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Rhode Island	ng/L	20.3	–	–	<20	81	USEPA, 2016d
Drinking water	N/A	PFOA	USA: South Carolina	ng/L	20.0	–	–	<20	24	USEPA, 2016d
Drinking water	N/A	PFOA	USA: South Dakota	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Tennessee	ng/L	20	–	–	<20	20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Texas	ng/L	20.0	–	–	<20	26.4	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Utah	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Vermont	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Virginia	ng/L	20.0	–	–	<20	22.2	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Washington	ng/L	20.0	–	–	<20	51.1	USEPA, 2016d
Drinking water	N/A	PFOA	USA: West Virginia	ng/L	21.7	–	–	<20	129	USEPA, 2016d

(*continued*)

EXHIBIT 13 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Drinking water	N/A	PFOA	USA: Wisconsin	ng/L	20.0	–	–	<20	43.17	USEPA, 2016d
Drinking water	N/A	PFOA	USA: Wyoming	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA Territory: Puerto Rico	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOA	USA Territory: Virgin Islands	ng/L	<20	–	–	<20	<20	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Alabama	ng/L	40.3	–	–	<40	180	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Alaska	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Arizona	ng/L	40.4	–	–	<40	300	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Arkansas	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: California	ng/L	40.1	–	–	<40	156	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Colorado	ng/L	42.7	–	–	<40	1,300	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Connecticut	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Delaware	ng/L	43.1	–	–	<40	1,800	USEPA, 2016d
Drinking water	N/A	PFOS	USA: District of Columbia (DC)	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Florida	ng/L	40.4	–	–	<40	380	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Georgia	ng/L	40.2	–	–	<40	120	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Hawaii	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Idaho	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Illinois	ng/L	40.0	–	–	<40	180	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Indiana	ng/L	40.1	–	–	<40	78.3	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Iowa	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Kansas	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Kentucky	ng/L	40.0	–	–	<40	58.53	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Louisiana	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Maine	ng/L	42.0	–	–	<40	290	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Maryland	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Massachusetts	ng/L	40.4	–	–	<40	430	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Michigan	ng/L	40.0	–	–	<40	60	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Minnesota	ng/L	40.7	–	–	<40	439	USEPA, 2016d

EXHIBIT 13 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Drinking water	N/A	PFOS	USA: Mississippi	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Missouri	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Montana	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Nebraska	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Nevada	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: New Hampshire	ng/L	40.4	–	–	<40	120	USEPA, 2016d
Drinking water	N/A	PFOS	USA: New Jersey	ng/L	40.1	–	–	<40	98	USEPA, 2016d
Drinking water	N/A	PFOS	USA: New Mexico	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: New York	ng/L	40.4	–	–	<40	530	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Navajo Nation	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: North Carolina	ng/L	40.1	–	–	<40	90	USEPA, 2016d
Drinking water	N/A	PFOS	USA: North Dakota	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Ohio	ng/L	40.5	–	–	<40	400	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Oklahoma	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Oregon	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Pennsylvania	ng/L	40.8	–	–	<40	1,090	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Region 1: Tribal	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Region 10: Tribal	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Region 5: Tribal	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Region 6: Tribal	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Region 8: Tribal	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Region 9: Tribal	ng/L	40.8	–	–	<40	120	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Rhode Island	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: South Carolina	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: South Dakota	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Tennessee	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Texas	ng/L	40.0	–	–	<40	46.16	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Utah	ng/L	<40	–	–	<40	<40	USEPA, 2016d

(*continued*)

EXHIBIT 13 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Drinking water	N/A	PFOS	USA: Vermont	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Virginia	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Washington	ng/L	40.2	–	–	<40	600	USEPA, 2016d
Drinking water	N/A	PFOS	USA: West Virginia	ng/L	40.6	–	–	<40	86.1	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Wisconsin	ng/L	40.1	–	–	<40	140	USEPA, 2016d
Drinking water	N/A	PFOS	USA: Wyoming	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA Territory: Puerto Rico	ng/L	<40	–	–	<40	<40	USEPA, 2016d
Drinking water	N/A	PFOS	USA Territory: Virgin Islands	ng/L	<40	–	–	<40	<40	USEPA, 2016d

ranged from 1.9 to 16.7 ng/mL, with individual data points with detections ranging from 3.92 to 34.8 ng/mL. Mean concentrations of PFOA ranged from 1.1 to 3.4 ng/mL, with individual data points with detections ranging from 0.3 to 7.1 ng/mL. No trends were noted due to the small sample size.

3.2.4 | Plasma

Four studies were identified (Kannan et al., 2004; Olsen et al., 2005, 2007, 2008) that contained human plasma results, and similarly to the human blood serum studies, these results were presented as a mixture of arithmetic and geometric mean concentrations. Mean PFOS concentrations ranged from 14.5 to 42.8 ng/mL, and individual data points with detections ranged from 6.6 to 83 ng/mL in three U.S. states. Mean PFOA concentrations ranged from 2.2 to 27.5 ng/mL, and individual results with detections ranged from 4.7 to 56 ng/mL. Male and female results were reported separately from one U.S. state. No trends were noted due to the small sample size.

Overall, human data for ambient levels of PFAS represent many different regions and subgroups. Awareness of risk perceptions and confidentiality needs are critical factors when applying the concept of background levels of PFAS in human media at a site-specific level.

3.2.5 | Whole body freshwater fish

Exhibit 23 presents a summary of the background data reported for fish and shellfish tissue, Exhibits 24 and 25 display the whole body fish and shellfish data and fish liver data on a scatter plot, and Exhibits 26 and 27 illustrate the fish and shellfish tissue data as geographically specific concentration ranges presented on a map of North America.

As shown in Exhibit 23, three studies were identified (Awad et al., 2011; De Silva et al., 2011; Kannan et al., 2005) that contained whole body freshwater fish results for PFOS and PFOA, one additional site with results for just PFOA (DuPont, 2008), and two sites with results for just PFOS (although some other PFAS were also detected) (Lanza et al., 2017; OECD, 2002). Five results reported from the Great Lakes exhibited mean concentrations of PFOS ranging from 2.3 to 96 μg/kg ww, while two results from Canada exhibited concentrations ranging from 13.6 to 58 μg/kg ww. A recent study from Air Force Base (AFB; Bossier City, Louisiana) reports geometric mean whole fish homogenate PFOS background concentrations at 113 μg/kg dw (Lanza et al., 2017; ww whole fish homogenate data may reflect lower PFAS levels). Five results reported from the Great Lakes, plus one additional U.S. result, exhibited mean concentrations of PFOA ranging from <0.42 to 1.83 μg/kg ww, while the two results from Canada exhibited concentrations ranging from <0.1 to 0.4 μg/kg ww.

The range in the whole body freshwater fish data for PFOS and PFOA is fairly narrow based on the mean concentrations reported from the few available studies (Exhibits 24 and 25), with less than two orders of magnitude difference between the range of means for PFOS and less than one order of magnitude difference between the range of means for PFOA. With one exception for PFOS in Eastern Lake Erie and the results observed at Barksdale AFB, mean and individual concentrations of PFOS and PFOA in whole body fish tissue samples are below the fish tissue RSL protective of human health (75.8 μg/kg ww based on a daily adult fish consumption rate of 22 grams per day) that is applicable to both PFOA and PFOS. However, whole fish residues are likely overly conservative estimates of human exposure and should be interpreted with caution.

Whole body fish tissue concentrations appear to be lower in Lake Superior, Lake Erie, and Lake Ontario samples relative to other locations with whole body fish tissue from the Great Lakes (Exhibits 26 and 27).

3.2.6 | Freshwater fish muscle, eggs, liver, heart, gonad, and digestive tract

Four studies were identified (Kannan et al., 2005; Lanza, 2015; RPA & BRE Environment, 2004; Sinclair et al., 2004) that contained results for PFOS in fish muscle, with concentrations ranging from <7 to 923 μg/kg ww. Kannan et al. (2005) also reported nondetect results for PFOA

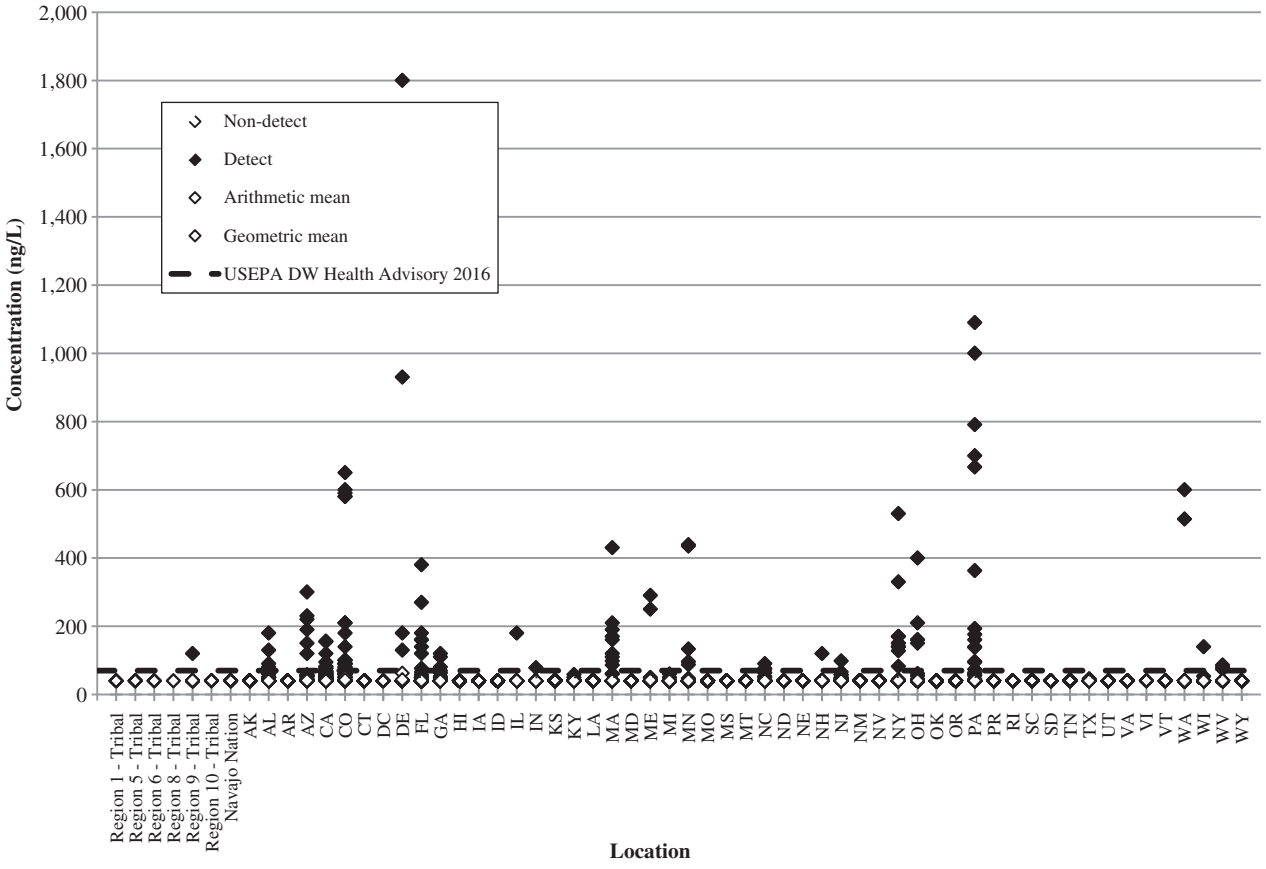


EXHIBIT 14 Locations in the United States and Canada with surface water background data for PFOA

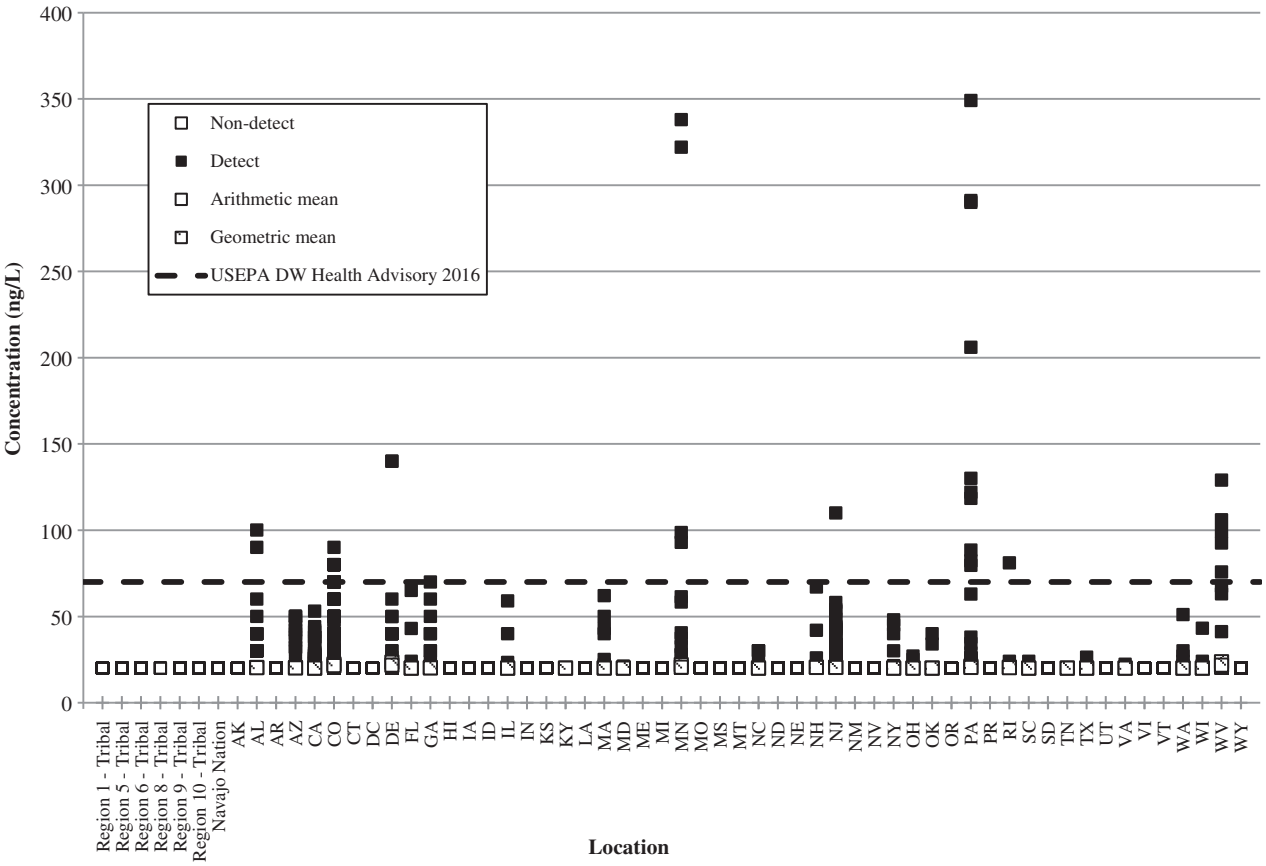


EXHIBIT 15 Scatter plot of drinking water background data for PFOS

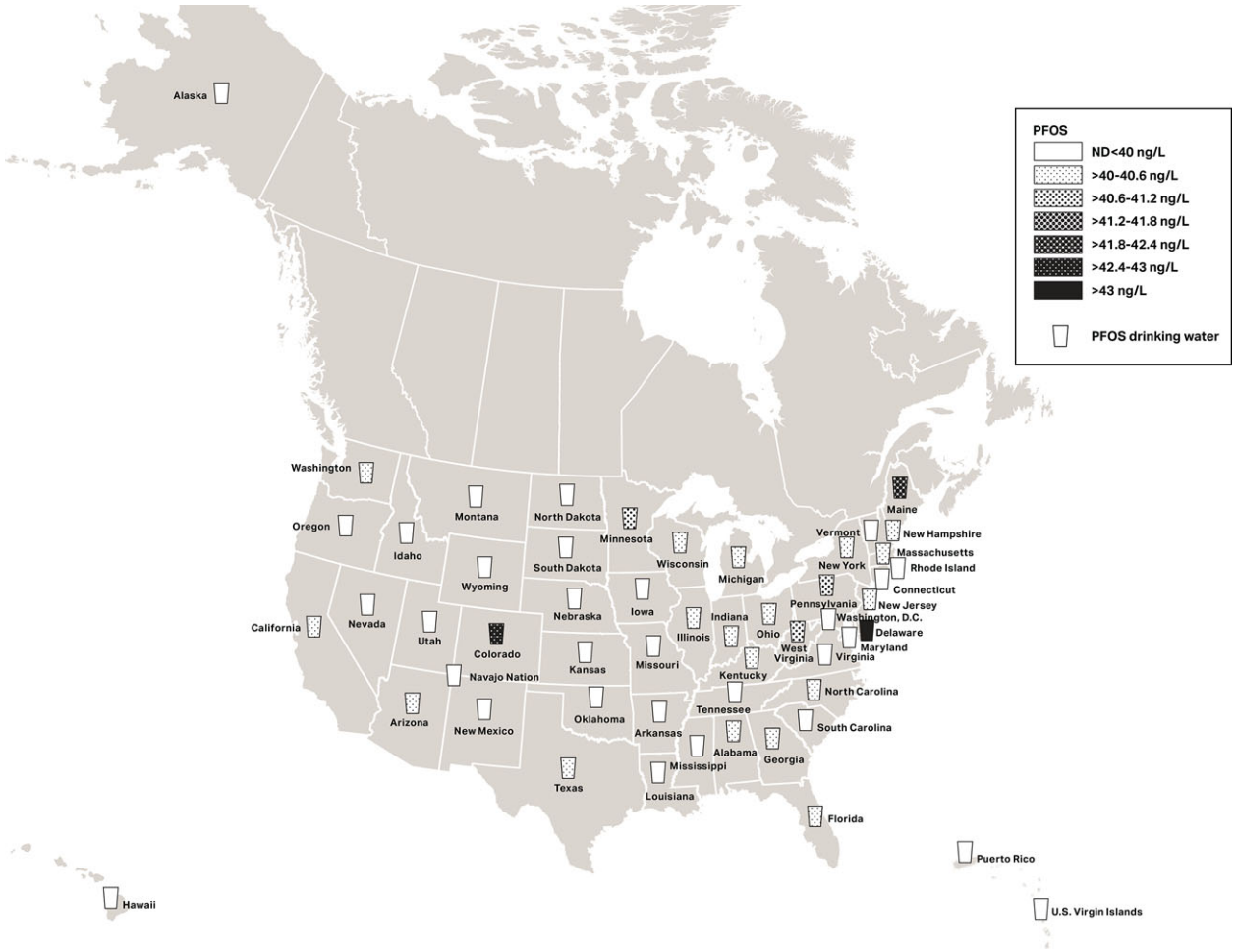


EXHIBIT 16 Scatter plot of drinking water background data for PFOA

in fish muscle at detection limits ranging from <0.2 to <2 μg/kg ww. One study (Giesy & Kannan, 2002) reported PFOS results in fish eggs of 250 μg/kg ww. Five studies (Awad et al., 2011; Lanza, 2015; Martin, Whittle, Muir, & Mabury, 2004; Sinclair et al., 2006, 2004) reported mean PFOS fish liver concentrations ranging from 5.7 to 2,226 μg/kg ww and individual data points ranging from 5.7 to 11,688 μg/kg ww. Awad et al. (2011), Sinclair et al. (2006), and Martin et al. (2004) also reported PFOA fish liver concentrations ranging from <1.5 to 6.1 μg/kg ww. One study (Lanza, 2015) reported mean PFOS fish concentrations measured in the heart (1,082 μg/kg ww), gonad (604 μg/kg ww), and digestive tract (189 μg/kg ww). Results with unknown locations were reviewed but not included in these concentration ranges. With a few exceptions, most of the freshwater fish tissue samples were collected from the Great Lakes Region.

Freshwater fish background data were most abundant for liver tissue, with the exception of the whole body data discussed earlier. With the exception of the background samples collected near Barksdale AFB, the spread in the fish liver data for PFOS is tight based on the mean concentrations reported from the few available studies (Exhibit 24), with less than one order of magnitude difference between the highest and lowest mean concentrations for PFOS, and more variability in the individual data points (greater than two orders of magnitude difference between the minimum and maximum detections). The individual data points reported for PFOA in fish liver are very tight (Exhibit 25). The fish tissue RSL of 75.8 μg/kg ww for PFOS and PFOA was exceeded by the maximum concentration of PFOS for all six media (muscle, eggs, liver, heart, gonad, and digestive tract) and the PFOA data (only available for muscle and liver) were well below the RSL. However, all mean concentrations of PFOS in fish liver are two times lower than the RSL, with the exception of the mean fish liver concentration from Barksdale AFB (approximately 30 times higher than the RSL). All mean PFOS concentrations from background fish tissues collected near this AFB (muscle, liver, heart, gonad, and digestive tract) exceeded the RSL.

3.2.7 | Freshwater invertebrates

Kannan et al. (2005) contained background results for PFOS in freshwater invertebrates (crustaceans and bivalves), with detected concentrations ranging from 2.4 to 4.3 μg/kg ww. This study also reported nondetect results for PFOA in freshwater invertebrates at detection limits ranging from <0.2 to <5 μg/kg ww. These samples were collected from two riverine systems in Michigan. One additional study was identified that reported an arithmetic mean concentration of PFOS of 15.7 μg/kg ww for freshwater bivalve samples collected in Alabama (RPA & BRE Environment, 2004).

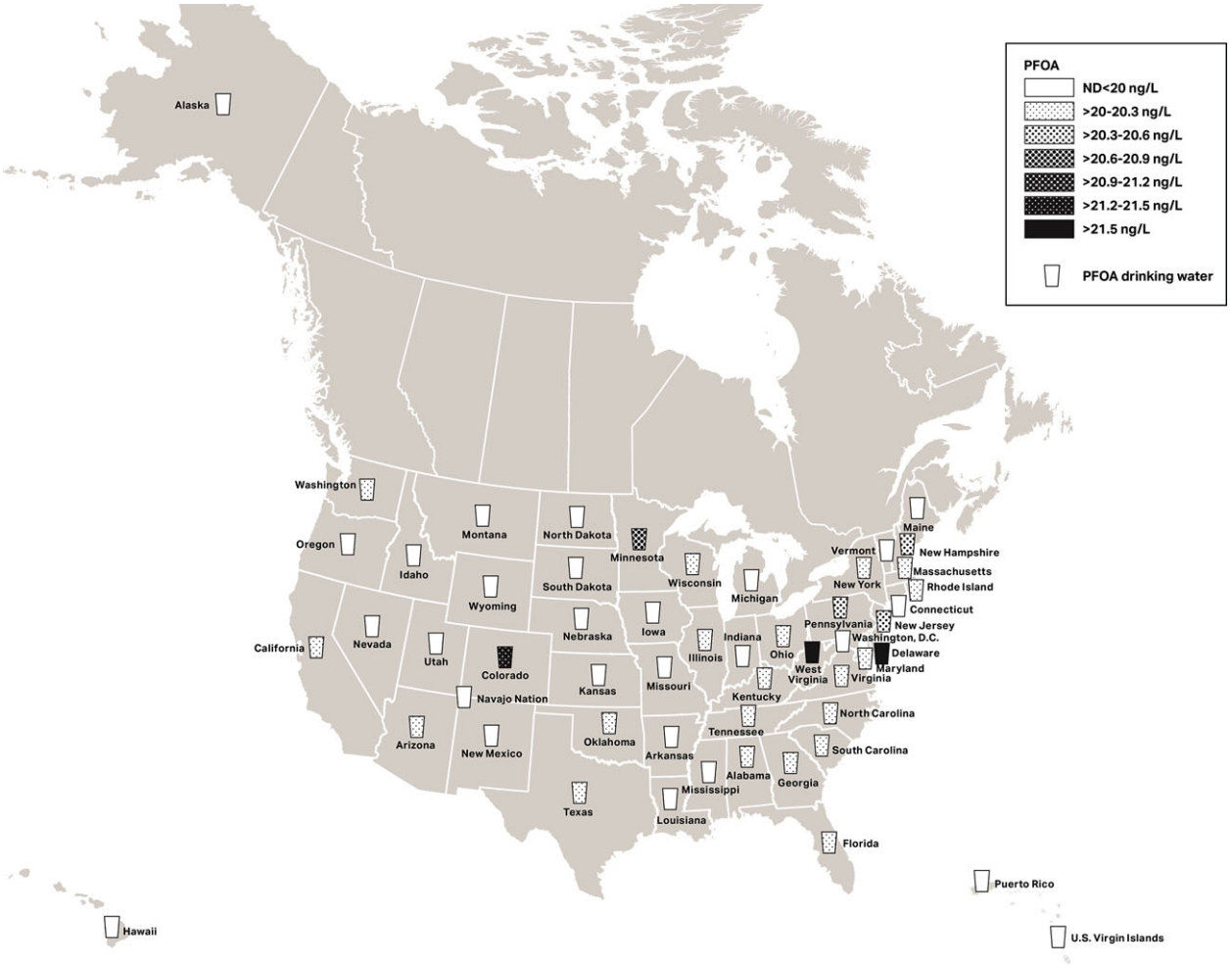


EXHIBIT 17 Locations in the United States and Canada with drinking water background data for PFOS

3.2.8 | Marine fish and shellfish

Two studies were identified (Powley, George, Russell, Hoke, & Buck, 2008; Tomy et al., 2004) that contained background PFOS and PFOA results for whole body marine fish samples, with detected concentrations of PFOS ranging from 0.3 to 4.7 μg/kg ww and one detected concentration of PFOA (0.5 μg/kg ww). These samples were collected from two Canadian provinces. Three studies were identified (Giesy & Kannan, 2002; Martin et al., 2004; Tomy et al., 2004) that contained PFOS results for marine fish liver, with detected concentrations ranging from 6.3 to 12 μg/kg ww and arithmetic mean concentrations of 1.2 and 12 μg/kg ww. These samples were collected from two Canadian provinces and the North Pacific Ocean. Tomy et al. (2004) and Martin et al. (2004) also provide PFOA results for marine fish liver; with one detection of 5.3 μg/kg ww out of 16 samples total ($n = 7$ in Tomy et al., 2004 and $n = 9$ in Martin et al., 2004).

Two studies (Kannan, Hansen, Wade, & Giesy, 2002; Tomy et al., 2004) were identified that contained PFOS concentrations in marine bivalves. Kannan et al. (2002) reported dw detected concentrations ranging from 331 to 1,225 μg/kg dw, and an arithmetic mean from eight locations ranging from 229 to 437 μg/kg dw. These samples were collected from seven U.S. states and one U.S. territory. Tomy et al. (2004) reported ww detected concentrations of PFOS in marine bivalves and crustaceans of 0.08 to 0.9 μg/kg ww from one Canadian province, and arithmetic mean concentrations of 0.28 μg/kg ww and 0.35 μg/kg ww. This study also reported a detected concentration of PFOA in marine crustaceans of 0.5 μg/kg ww and an arithmetic mean concentration of 0.17 μg/kg ww. All marine fish and shellfish data provided in ww demonstrate concentrations are well below the fish tissue RSL of 75.8 μg/kg ww for PFOS and PFOA, while the dw data reported for marine bivalves exceed the RSL by more than one order of magnitude (Exhibits 24 and 25).

PFOS concentrations in marine shellfish collected from Texas, Mississippi, and Puerto Rico (Caribbean Sea) are notably higher than in the available marine and freshwater fin fish samples (Exhibit 26). However, it is important to note that these high shellfish tissue concentrations may also be an artifact of the dw PFOS concentrations reported for shellfish and ww concentrations reported for fin fish (ww data for shellfish may reflect lower PFAS levels). In general, fish and invertebrate tissue data are among the easiest to collect and evaluate when applying the concept of background PFAS levels at contaminated sites.

EXHIBIT 18 Tabular summary of human tissue background studies – whole blood, serum, umbilical cord blood, plasma

Medium	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Blood serum	PFOA	Canada: Edmonton, AB	ng/mL	1.3	2.1	1.5	<0.25	18	Hamm et al., 2010
Blood serum	PFOA	Canada: Hamilton, ON	ng/mL	–	2.54	2.13	1.46	3.14	Monroy et al., 2008
Blood serum	PFOA	Canada: Hamilton, ON	ng/mL	–	2.24	1.81	1.33	2.64	Monroy et al., 2008
Blood serum	PFOA	Canada: Northern Canada	ng/mL	–	2.2	–	–	–	Tittlemier et al., 2004
Blood serum	PFOA	Canada: Ottowa, ON, and Gatineau, QC	ng/mL	–	3.4	–	<1.2	7.2	Kubwabo et al., 2004
Blood serum	PFOA	Canada: Vancouver, BC	ng/mL	–	1.8	–	–	–	Beesoon et al., 2011
Blood serum	PFOA	USA	ng/mL	–	6.4	–	<5	35.2	Hansen et al., 2001
Blood serum	PFOA	USA	ng/mL	5.21	–	–	–	–	CDC, 2017
Blood serum	PFOA	USA	ng/mL	4.9	5.6	5.1	<1.9	56.1	Olsen et al., 2004a
Blood serum	PFOA	USA	ng/mL	–	3	–	1	13	ToxConsultant, 2014
Blood serum	PFOA	USA	ng/mL	–	17	–	12	22	ToxConsultant, 2014
Blood serum	PFOA	USA	ng/mL	–	2.08	–	–	–	Calafat et al., 2006a
Blood serum	PFOA	USA	ng/mL	–	2.85	–	–	–	Calafat et al., 2006a
Blood serum	PFOA	USA	ng/mL	9.6	–	11.6	2.8	23.7	Calafat et al., 2006b
Blood serum	PFOA	USA	ng/mL	–	3.97	–	–	–	Calafat et al., 2006a
Blood serum	PFOA	USA	ng/mL	–	2.89	–	–	–	Calafat et al., 2006a
Blood serum	PFOA	USA	ng/mL	–	3.62	–	–	–	Calafat et al., 2006a
Blood serum	PFOA	USA	ng/mL	–	6.98	–	–	–	Calafat et al., 2006a
Blood serum	PFOA	USA	ng/mL	3.95	–	–	<0.1	77.2	CDC, 2017
Blood serum	PFOA	USA	ng/mL	3.92	–	–	–	–	CDC, 2017
Blood serum	PFOA	USA	ng/mL	4.12	–	–	–	–	CDC, 2017
Blood serum	PFOA	USA	ng/mL	3.07	–	–	–	–	CDC, 2017
Blood serum	PFOA	USA	ng/mL	2.08	–	–	–	–	CDC, 2017
Blood serum	PFOA	USA	ng/mL	1.94	–	–	–	–	CDC, 2017
Blood serum	PFOA	USA	ng/mL	2.5	3.1	–	<3.0	7	Olsen et al., 2003b
Blood serum	PFOA	USA	ng/mL	–	6.125–7.575	–	–	–	Kato et al., 2009
Blood serum	PFOA	USA: (mothers) San Francisco, CA	ng/mL	0.47	–	–	<0.30	>1.25	Biomonitoring California, 2015b

(*continued*)

EXHIBIT 18 (Continued)

Medium	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Blood serum	PFOA	USA: Atlanta, GA	ng/mL	4.0	4.9	–	0.2	10.4	Kuklenyik et al., 2004
Blood serum	PFOA	USA: Baltimore, MD	ng/mL	1.6	–	1.6	–	–	Apelberg et al., 2007
Blood serum	PFOA	USA: Baltimore, MD	ng/mL	1.5	–	1.6	–	–	Apelberg et al., 2007
Blood serum	PFOA	USA: Baltimore, MD	ng/mL	1.5	–	1.4	–	–	Apelberg et al., 2007
Blood serum	PFOA	USA: Boston, MA	ng/mL	5.4	–	5.5	1.5	13.9	Olsen et al., 2003a
Blood serum	PFOA	USA: Charlotte, NC	ng/mL	6.3	–	6.3	<2.1	29	Olsen et al., 2003a
Blood serum	PFOA	USA: Hagerstown, MD	ng/mL	4.2	–	4.7	<2.1	52.3	Olsen et al., 2003a
Blood serum	PFOA	USA: Hoosick Falls area, NY	ng/mL	23.5	–	–	–	–	NYSDOH, 2016
Blood serum	PFOA	USA: Los Angeles, CA	ng/mL	4.1	–	4.6	<2.1	34.1	Olsen et al., 2003a
Blood serum	PFOA	USA: MI	ng/mL	–	5.1	–	<3	14.7	Kannan et al., 2003
Blood serum	PFOA	USA: Midwest	ng/mL	–	1.7	–	–	–	D'eon et al., 2009
Blood serum	PFOA	USA: Midwest	ng/mL	–	4.4	–	0.9	8.6	De Silva & Mabury, 2006
Blood serum	PFOA	USA: Midwest	ng/mL	–	4.2	–	–	–	D'eon et al., 2009
Blood serum	PFOA	USA: Portland, OR	ng/mL	3.6	–	3.8	<2.1	16.7	Olsen et al., 2003a
Blood serum	PFOA	USA: Seattle, WA	ng/mL	4.2	–	4.2	<1.4	16.7	Olsen et al., 2004b
Blood serum	PFOA	USA: St. Paul, MN	ng/mL	4.5	5.2	4.4	<1.92	20	Olsen et al., 2007
Blood serum	PFOA	USA: Teachers, CA	ng/mL	2.46	–	–	<0.029	>6.22	Biomonitoring California, 2015a
Blood serum	PFOS	Canada: Edmonton, AB	ng/mL	7.4	9	7.8	<0.25	35	Hamm et al., 2010
Blood serum	PFOS	Canada: Hamilton, ON	ng/mL	–	16.19	14.54	9.19	20.22	Monroy et al., 2008
Blood serum	PFOS	Canada: Hamilton, ON	ng/mL	–	18.31	16.6	10.8	22.9	Monroy et al., 2008
Blood serum	PFOS	Canada: Northern Canada	ng/mL	–	36.9	–	–	–	Tittlemier et al., 2004
Blood serum	PFOS	Canada: Ottowa, ON, and Gatineau, QC	ng/mL	–	28.8	–	3.7	65.1	Kubwabo et al., 2004
Blood serum	PFOS	Canada: Vancouver, BC	ng/ml	–	5.5	–	–	–	Beesoon et al., 2011
Blood serum	PFOS	USA	ng/mL	30	–	31.1	13.8	56.5	Calafat et al., 2006b
Blood serum	PFOS	USA	ng/mL	30.4	–	–	–	–	CDC, 2017
Blood serum	PFOS	USA	ng/mL	–	10.4	–	–	–	Calafat et al., 2006a
Blood serum	PFOS	USA	ng/mL	–	17.93	–	–	–	Calafat et al., 2006a
Blood serum	PFOS	USA	ng/mL	–	23.97	–	–	–	Calafat et al., 2006a

(*continued*)

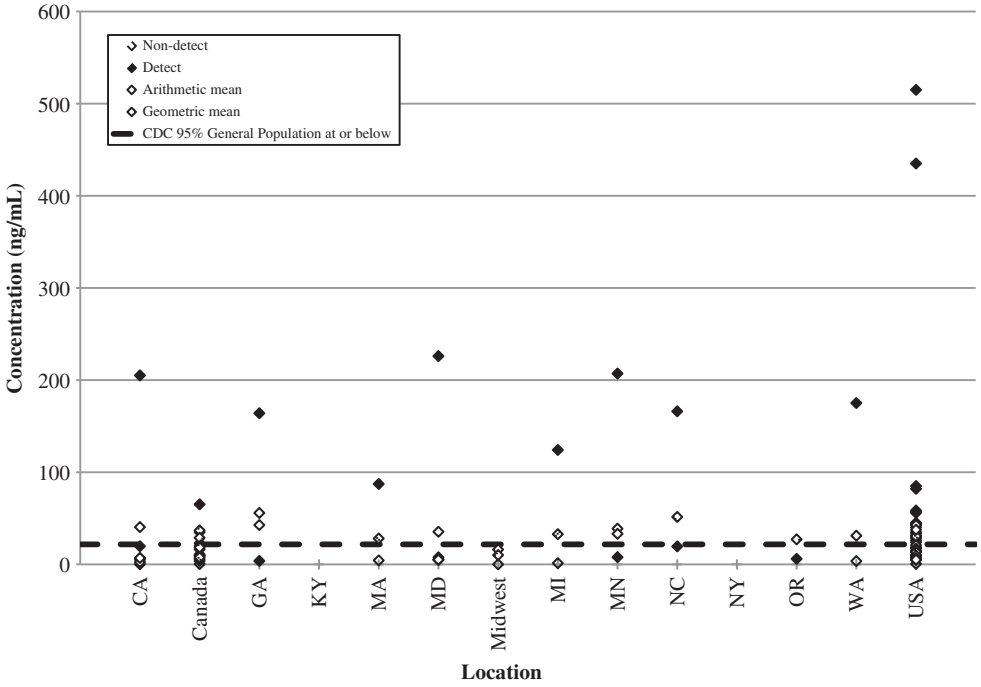
EXHIBIT 18 (Continued)

Medium	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Blood serum	PFOS	USA	ng/mL	–	13.71	–	–	–	Calafat et al., 2006a
Blood serum	PFOS	USA	ng/mL	–	18.27	–	–	–	Calafat et al., 2006a
Blood serum	PFOS	USA	ng/mL	–	40.19	–	–	–	Calafat et al., 2006a
Blood serum	PFOS	USA	ng/mL	20.7	–	–	<0.4	435	CDC, 2017
Blood serum	PFOS	USA	ng/mL	17.1	–	–	–	–	CDC, 2017
Blood serum	PFOS	USA	ng/mL	14.7	17.7	–	<6.1	58.3	Olsen et al., 2003b
Blood serum	PFOS	USA	ng/mL	37.5	43.5	36.7	6.7	515	Olsen et al., 2004a
Blood serum	PFOS	USA	ng/mL	–	44	–	43	44	OECD, 2002
Blood serum	PFOS	USA	ng/mL	–	33	–	26	45	OECD, 2002
Blood serum	PFOS	USA	ng/mL	–	35	–	5	85	OECD, 2002
Blood serum	PFOS	USA	ng/mL	–	29.7	–	9	56	OECD, 2002
Blood serum	PFOS	USA	ng/mL	–	28.4	–	6.7	82	Hansen et al., 2001
Blood serum	PFOS	USA	ng/mL	13.2	–	–	–	–	CDC, 2017
Blood serum	PFOS	USA	ng/mL	9.32	–	–	–	–	CDC, 2017
Blood serum	PFOS	USA	ng/mL	6.31	–	–	–	–	CDC, 2017
Blood serum	PFOS	USA	ng/mL	4.99	–	–	–	–	CDC, 2017
Blood serum	PFOS	USA	ng/mL	–	30.45–42.45	–	–	–	Kato et al., 2009
Blood serum	PFOS	USA: (mothers) San Francisco, CA	ng/mL	2.55	–	–	–	>4.9	Biomonitoring California, 2015b
Blood serum	PFOS	USA: Atlanta, GA	ng/mL	43	55.8	–	3.6	164	Kuklenyik et al., 2004
Blood serum	PFOS	USA: Baltimore, MD	ng/mL	4.9	–	5	–	–	Apelberg et al., 2007
Blood serum	PFOS	USA: Baltimore, MD	ng/mL	4.9	–	5	–	–	Apelberg et al., 2007
Blood serum	PFOS	USA: Baltimore, MD	ng/mL	5	–	4.1	–	–	Apelberg et al., 2007
Blood serum	PFOS	USA: Boston, MA	ng/mL	28	–	29.5	<4.3	87.2	Olsen et al., 2003a
Blood serum	PFOS	USA: Charlotte, NC	ng/mL	51.5	–	48.9	19.3	166	Olsen et al., 2003a
Blood serum	PFOS	USA: Hagerstown, MD	ng/mL	35.3	–	35.7	7.6	226	Olsen et al., 2003a
Blood serum	PFOS	USA: Los Angeles, CA	ng/mL	40.4	–	42.2	6.6	205	Olsen et al., 2003a
Blood serum	PFOS	USA: MI	ng/mL	–	32.6	–	<1.3	124	Kannan et al., 2003

(*continued*)

EXHIBIT 18 (Continued)

Medium	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Blood serum	PFOS	USA: Midwest	ng/mL	–	16	–	–	–	D'eon et al., 2009
Blood serum	PFOS	USA: Midwest	ng/mL	–	10	–	–	–	D'eon et al., 2009
Blood serum	PFOS	USA: Midwest	ng/mL	–	N/A	–	–	–	ATSDR, 2015
Blood serum	PFOS	USA: Portland, OR	ng/mL	27	–	26	6	1,656	Olsen et al., 2003a
Blood serum	PFOS	USA: Seattle, WA	ng/mL	31	–	30.2	<3.4	175	Olsen et al., 2004b
Blood serum	PFOS	USA: St. Paul, MN	ng/mL	33.1	38.6	31.7	7.7	207	Olsen et al., 2007
Blood serum	PFOS	USA: Teachers, CA	ng/mL	6.8	–	–	<0.083	>19.5	Biomonitoring California, 2015a
Liver	PFOA	USA	μg/kg ww	–	–	–	<17.9	47	Olsen et al., 2003b
Liver	PFOS	USA	μg/kg ww	15.3	18.8	–	<4.5	57	Olsen et al., 2003b
Plasma	PFOA	USA	ng/mL	3.4	3.9	3.6	<1	28.1	Olsen et al., 2008
Plasma	PFOA	USA: NYC, NY	ng/mL	–	27.5	25.2	14	56	Kannan et al., 2004
Plasma	PFOA	USA: St. Paul, MN	ng/mL	2.2	2.4	2.4	<1.01	4.7	Olsen et al., 2007
Plasma	PFOA	USA: Washington County, MD	ng/mL	5.5	–	5.6	–	–	Olsen et al., 2005
Plasma	PFOS	USA	ng/mL	14.5	16.9	14.2	<2.5	77.9	Olsen et al., 2008
Plasma	PFOS	USA: NYC, NY	ng/mL	–	42.8	42	16	83	Kannan et al., 2004
Plasma	PFOS	USA: St. Paul, MN	ng/mL	15.1	16.3	15.8	6.6	36.9	Olsen et al., 2007
Plasma	PFOS	USA: Washington County, MD	ng/mL	33.3	–	34.7	–	–	Olsen et al., 2005
Umbilical cord blood	PFOA	Canada: Hamilton, ON	ng/mL	–	1.94	1.58	1.09	2.37	Monroy et al., 2008
Umbilical cord blood	PFOA	Canada: Northern Canada	ng/mL	–	3.4	–	–	–	Tittlemier et al., 2004
Umbilical cord blood	PFOA	Canada: Vancouver, BC	ng/mL	–	1.1	–	–	–	Beesoon et al., 2011
Umbilical cord blood	PFOA	USA: Baltimore, MD	ng/mL	1.6	–	1.6	0.3	7.1	Apelberg et al., 2007
Umbilical cord blood	PFOS	Canada: Hamilton, ON	ng/mL	–	7.19	6.08	3.92	9.11	Monroy et al., 2008
Umbilical cord blood	PFOS	Canada: Northern Canada	ng/mL	–	16.7	–	–	–	Tittlemier et al., 2004
Umbilical cord blood	PFOS	Canada: Vancouver, BC	ng/mL	–	1.8	–	–	–	Beesoon et al., 2011
Umbilical cord blood	PFOS	USA: Baltimore, MD	ng/mL	4.9	–	5	<0.2	34.8	Apelberg et al., 2007
Whole blood	PFOA	USA: KY	ng/mL	–	23	20	15	39	Kannan et al., 2004
Whole blood	PFOA	USA: KY	ng/mL	–	41.6	38.1	11	88	Kannan et al., 2004
Whole blood	PFOS	USA: KY	ng/mL	–	66	81	11	130	Kannan et al., 2004
Whole blood	PFOS	USA: KY	ng/mL	–	73.2	72	19	164	Kannan et al., 2004



Maximum concentration in OR was 1,656 ng/mL and is likely an outlier.

EXHIBIT 19 Locations in the United States and Canada with drinking water background data for PFOA

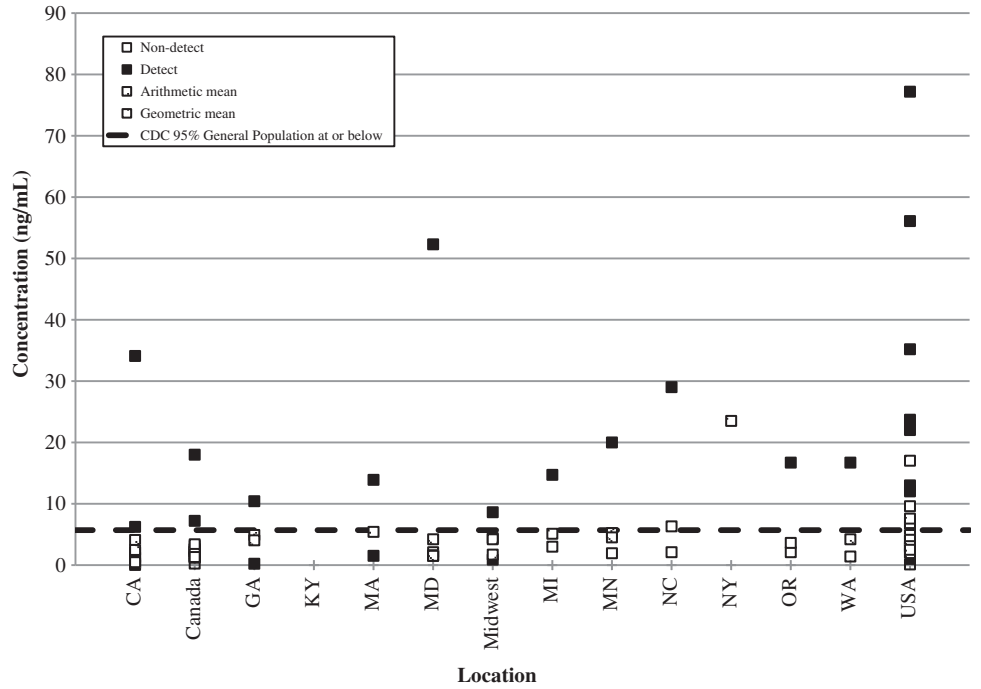


EXHIBIT 20 Scatter plot of blood serum background data for PFOS

3.3 | Implications of considering background and ambient levels of PFAS

These background results are useful both at small and larger scales of understanding PFAS distribution trends. Unlike naturally-occurring metals or PAHs, which may arise from both natural and anthropogenic sources, PFAS are wholly synthetic compounds. Thus, their occurrence in the environment is an indication of their multiple sources, widespread use, long-range transport, and persistence. This has implications when considering PFAS in the context of site characterization, risk assessment, and remediation at contaminated sites.

The conceptual site model for a contaminated site may include on-site source areas accompanied by transport to offsite areas. However, while PFAS concentrations in soils and groundwater may be elevated in the vicinity of the source area, they often decrease to much lower concentrations in off-site areas. In order to establish a robust

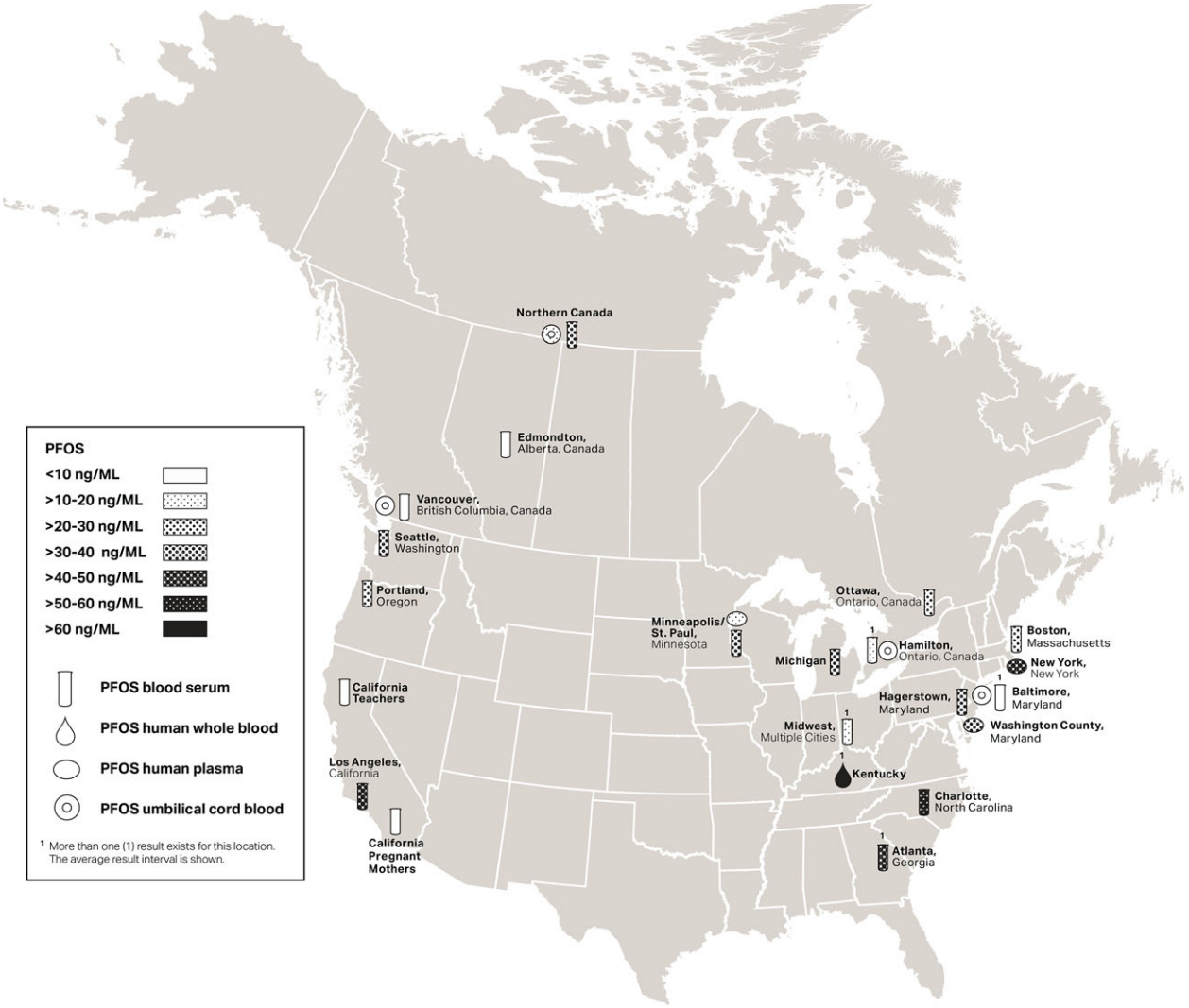


EXHIBIT 21 Scatter plot of blood serum background data for PFOA

and reliable demarcation of releases and plume boundaries, it is beneficial to determine upgradient, upstream, or reference area concentrations of PFAS, particularly in urban areas where other sources of PFAS may also lend to releases to surface water (e.g., storm drain discharges and wastewater treatment plant effluent releases). Without such background characterization, the area impacted by a particular known source may be assumed to be larger than necessary. Risk assessments for individual sites may overestimate site-related risks by not considering risks related to background exposures, particularly for dietary pathways such as fish consumption. Human data may also be useful in certain situations. In a recently completely risk assessment for a PFAS site in Australia, more than 60 publications from 2003 to 2015 were reviewed to establish expected background concentrations of PFOA in blood serum in populations that were not occupationally exposed to PFAS, did not live near factories that manufactured or handled PFAS, and were not exposed to environmental contamination such as drinking water or fish (AECOM, 2016). It was demonstrated that PFOA in de-identified serum samples from a monitored community were lower than the expected background level of 25 ng/mL and that it was unlikely to be a site-related chemical of potential concern. It was also demonstrated that PFOS in the monitored community was higher than expected background levels of less than 50 ng/mL (AECOM, 2016). This demonstration allows effective risk management decisions to be made with a greater understanding of background and site-related contributions to risk.

In particular, the potential exists for background PFAS concentrations to contribute to surface water levels (e.g., Konwick et al., 2008; Simcik & Dorweiler, 2005) such that they may exceed the very low drinking water health advisory values in groundwater or surface waters whose designated beneficial uses included potable water supply (e.g., Kim & Kannan, 2007). In such cases, remediation or risk management efforts targeted to an individual site-related source may be more stringent or extensive than warranted and yet be ineffective in bringing the overall concentration below the target cleanup goals.

On a larger scale, these data for both environmental and biological media illustrate well-known facts about the ubiquity of PFAS, attributed to multiple sources and uses, long-range transport, and persistence in the environment. With the focus on phaseout of long-chain PFAS in products and replacement by short-chain PFAS and non-PFAS substitutes, background data serve as a monitor of overall PFAS trends

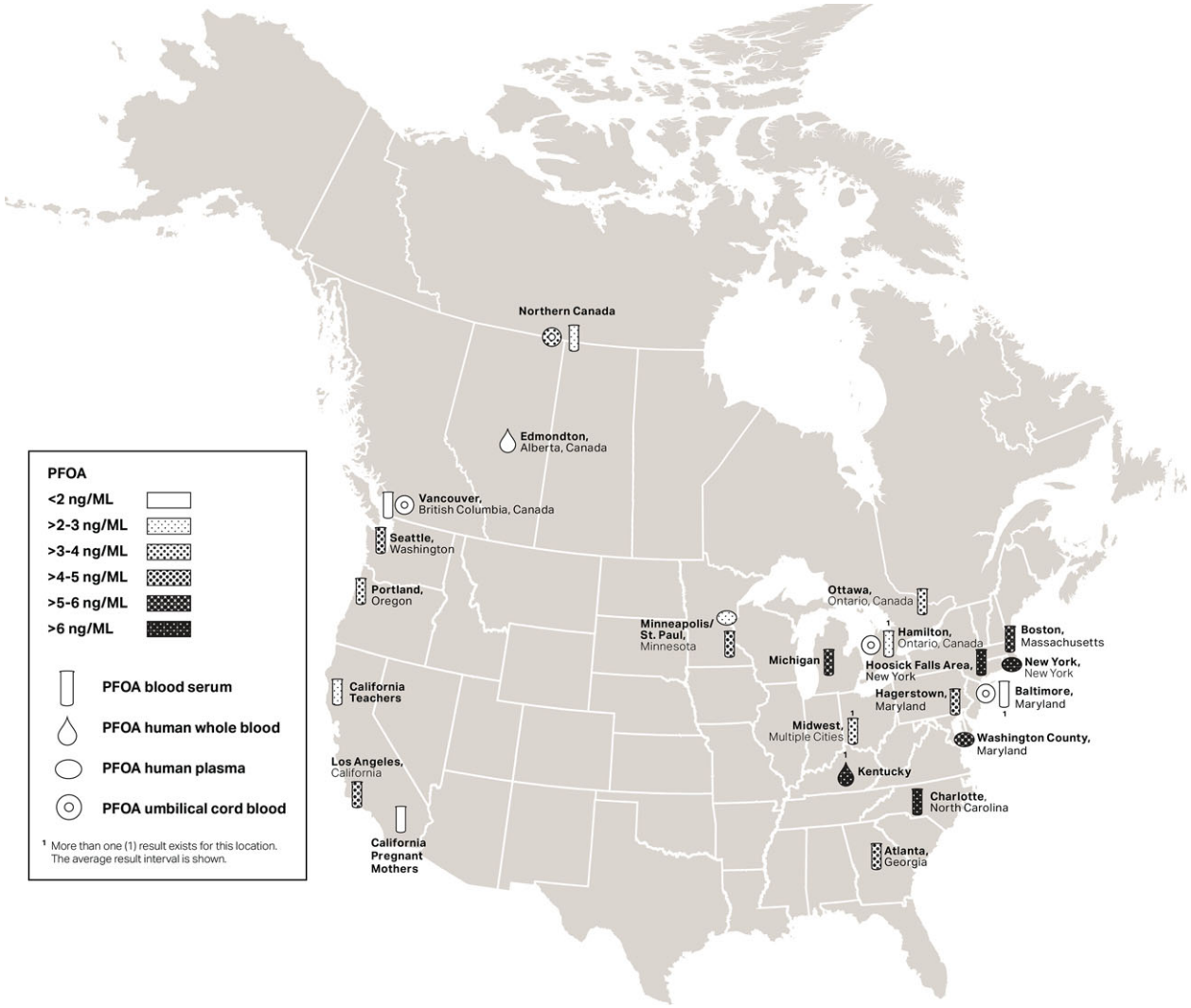


EXHIBIT 22 Locations in the United States and Canada with human tissue background data for PFOS: whole blood, serum, umbilical cord blood, plasma

and are used by some countries to assist in policy development (Environment and Climate Change Canada, 2017; Government of Western Australia, 2016) . For example, Wang, Cousins, Scheringer, and Hungerbuhler (2014) report several studies documenting increased levels of short-chain PFAS such as perfluorobutane sulfonate and perfluorobutanoic acid in surface waters in Germany, Japan, and the North Atlantic. Similarly, increasing trends have been reported for the short-chain perfluorobutane sulfonate and perfluorohexanoicsulfonate in the blood serum of Swedish women from 1996 to 2010 and in U.S. women since 2006 (Wang et al., 2014). By monitoring both long-chain and short-chain PFAS in the environment, regional, national or global trends in use and release may be discerned and follow-up measures may be taken as needed.

4 | CONCLUSIONS

Of the abiotic media evaluated in this study representative of background conditions (i.e., soil, sediment, and surface water), as well as drinking water, the most data were identified for drinking water, followed by soil and surface water. For all the data reported in this search, the potential for known or unknown sources of PFAS to influence "background" results should be recognized, especially for the drinking water dataset (UCMR3 data; USEPA, 2016d).

Most of the PFAS background data for surface water were collected from freshwater bodies, primarily from the Great Lakes region, with other samples from (mostly) the eastern United States. In addition, deep samples collected from the Pacific Ocean and samples from the northern Atlantic Ocean provide insight into background concentrations in marine environments. PFOS and PFOA concentrations measured in these marine samples are notably lower than in the freshwater body samples, especially for the deep Pacific data. More surface water data, especially from marine coastal areas and freshwater bodies outside of the Great Lakes region, would strengthen the level of confidence in the background dataset gathered for surface water in the United States.

Although fewer studies were found for other abiotic media, such as soil and sediment, the relatively recent Rankin et al. (2016)

EXHIBIT 23 Tabular summary of fish and shellfish tissue background studies: whole body, muscle, eggs, liver

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Fish liver	Freshwater	PFOA	Canada: Kuujjuarapik, QC	μg/kg ww	–	<2	–	<2	<2	Martin et al., 2004
Fish liver	Freshwater	PFOA	Canada: Kuujjuarapik, QC	μg/kg ww	–	<2	–	<2	<2	Martin et al., 2004
Fish liver	Freshwater	PFOA	Canada: Kuujjuarapik, QC	μg/kg ww	–	<2	–	<2	<2	Martin et al., 2004
Fish liver	Freshwater	PFOA	Canada: Kuujjuarapik, QC	μg/kg ww	–	<2	–	<2	<2	Martin et al., 2004
Fish liver	Freshwater	PFOA	Canada: Lac Minto, QC	μg/kg ww	–	<2	–	<2	<2	Martin et al., 2004
Fish liver	Freshwater	PFOA	Canada: Toronto, ON	μg/kg ww	–	–	–	<LOD	2.5	Awad et al., 2011
Fish liver	Freshwater	PFOA	USA: Franklin County, NY	μg/kg ww	–	–	–	<1.5	5	Sinclair et al., 2006
Fish liver	Freshwater	PFOA	USA: Jefferson County, NY	μg/kg ww	–	–	–	<1.5	6.1	Sinclair et al., 2006
Fish liver	Freshwater	PFOA	USA: Lewis County, NY	μg/kg ww	–	–	–	<1.5	5.2	Sinclair et al., 2006
Fish liver	Freshwater	PFOA	USA: St. Lawrence County, NY	μg/kg ww	–	–	–	<1.5	4.8	Sinclair et al., 2006
Fish liver	Freshwater	PFOS	Canada: Kuujjuarapik, QC	μg/kg ww	–	7.6	–	6.5	8.6	Martin et al., 2004
Fish liver	Freshwater	PFOS	Canada: Kuujjuarapik, QC	μg/kg ww	–	39	–	29	50	Martin et al., 2004
Fish liver	Freshwater	PFOS	Canada: Kuujjuarapik, QC	μg/kg ww	–	12	–	12	12	Martin et al., 2004
Fish liver	Freshwater	PFOS	Canada: Kuujjuarapik, QC	μg/kg ww	–	5.7	–	5.7	5.7	Martin et al., 2004
Fish liver	Freshwater	PFOS	Canada: Lac Minto, QC	μg/kg ww	–	31	–	31	31	Martin et al., 2004
Fish liver	Freshwater	PFOS	Canada: Toronto, ON	μg/kg ww	–	–	–	58	630	Awad et al., 2011
Fish liver	Freshwater	PFOS	USA: Franklin County, NY	μg/kg ww	–	–	–	16	120	Sinclair et al., 2006
Fish liver	Freshwater	PFOS	USA: Jefferson County, NY	μg/kg ww	–	–	–	14	75	Sinclair et al., 2006
Fish liver	Freshwater	PFOS	USA: Lewis County, NY	μg/kg ww	–	–	–	41	114	Sinclair et al., 2006
Fish liver	Freshwater	PFOS	USA: MI	μg/kg ww	–	–	–	<7.7	173	Sinclair et al., 2004
Fish liver	Freshwater	PFOS	USA: St. Lawrence County, NY	μg/kg ww	–	–	–	45	207	Sinclair et al., 2006
Fish liver	Freshwater	PFOS	USA: Bossier City, LA	μg/kg ww	980	2,226	–	263	11,688	Lanza, 2015
Fish liver	Marine	PFOA	Canada: Davis Strait, NU	μg/kg ww	–	1.2	–	<0.2	5.3	Tomy et al., 2004
Fish liver	Marine	PFOA	Canada: Kuujjuarapik, QC	μg/kg ww	–	<2	–	<2	<2	Martin et al., 2004
Fish liver	Marine	PFOS	Canada: Davis Strait, NU	μg/kg ww	–	1.4	–	<0.06	6.3	Tomy et al., 2004
Fish liver	Marine	PFOS	Canada: Kuujjuarapik, QC	μg/kg ww	–	12	–	12	12	Martin et al., 2004
Fish liver	Marine	PFOS	North Pacific Ocean	μg/kg ww	–	–	–	<7.0	<7.0	Giesy & Kannan, 2002

(*continued*)

EXHIBIT 23 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Whole fish	Freshwater	PFOA	Canada: Toronto, ON	μg/kg ww	–	–	–	<0.1	0.4	Awad et al., 2011
Whole fish	Freshwater	PFOA	USA: Calumet River, MI	μg/kg ww	–	–	–	<0.2	<0.2	Kannan et al., 2005
Whole fish	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<0.2	<2	Kannan et al., 2005
Whole fish	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<0.2	<0.2	Kannan et al., 2005
Whole fish	Freshwater	PFOA	USA: Lake Erie (eastern)	μg/kg ww	–	<0.42	–	–	–	De Silva et al., 2011
Whole fish	Freshwater	PFOA	USA: Lake Erie (western)	μg/kg ww	–	0.5	–	–	–	De Silva et al., 2011
Whole fish	Freshwater	PFOA	USA: Lake Huron	μg/kg ww	–	<0.42	–	–	–	De Silva et al., 2011
Whole fish	Freshwater	PFOA	USA: Lake Ontario	μg/kg ww	–	0.88	–	–	–	De Silva et al., 2011
Whole fish	Freshwater	PFOA	USA: Lake Superior	μg/kg ww	–	<0.42	–	–	–	De Silva et al., 2011
Whole fish	Freshwater	PFOA	USA: WV	μg/kg ww	–	1.83410701	–	–	–	DuPont, 2008
Whole fish	Freshwater	PFOS	USA: Bossier City, LA	μg/kg dw	113	138	–	6	393	Lanza et al., 2002
Whole fish	Freshwater	PFOS	Canada: Toronto, ON	μg/kg ww	–	–	–	13.6	58	Awad et al., 2011
Whole fish	Freshwater	PFOS	USA: Calumet River, MI	μg/kg ww	–	–	–	4.1	4.1	Kannan et al., 2005
Whole fish	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	6.6	11.2	Kannan et al., 2005
Whole fish	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	7.7	21.5	Kannan et al., 2005
Whole fish	Freshwater	PFOS	USA: Decatur, AL	μg/kg ww	–	59.1	–	–	–	OECD, 2002
Whole fish	Freshwater	PFOS	USA: Lake Erie (eastern)	μg/kg ww	–	96	–	–	–	De Silva et al., 2011
Whole fish	Freshwater	PFOS	USA: Lake Erie (western)	μg/kg ww	–	54	–	–	–	De Silva et al., 2011
Whole fish	Freshwater	PFOS	USA: Lake Huron	μg/kg ww	–	17	–	–	–	De Silva et al., 2011
Whole fish	Freshwater	PFOS	USA: Lake Ontario	μg/kg ww	–	52	–	–	–	De Silva et al., 2011
Whole fish	Freshwater	PFOS	USA: Lake Superior	μg/kg ww	–	2.3	–	–	–	De Silva et al., 2011
Whole fish	Marine	PFOA	Canada: Beaufort Sea, NWT	μg/kg	–	–	–	<0.2	<0.2	Powley et al., 2008
Whole fish	Marine	PFOA	Canada: Davis Strait, NU	μg/kg ww	–	0.16	–	<0.2	0.5	Tomy et al., 2004
Whole fish	Marine	PFOS	Canada: Beaufort Sea, NWT	μg/kg	–	–	–	0.3	0.7	Powley et al., 2008
Whole fish	Marine	PFOS	Canada: Davis Strait, NU	μg/kg ww	–	1.3	–	0.3	4.7	Tomy et al., 2004
Bivalves	Freshwater	PFOA	USA: Calumet River, MI	μg/kg ww	–	–	–	<5	<5	Kannan et al., 2005
Bivalves	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<5	<5	Kannan et al., 2005
Bivalves	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<5	<5	Kannan et al., 2005
Bivalves	Freshwater	PFOS	USA: Calumet River, MI	μg/kg ww	–	–	–	<2	<2	Kannan et al., 2005

(*continued*)

EXHIBIT 23 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Bivalves	Freshwater	PFOS	USA: Decatur, AL	μg/kg ww	–	15.6	–	–	–	RPA & BRE Environment, 2004
Bivalves	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	<2	3.1	Kannan et al., 2005
Bivalves	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	<2	<2	Kannan et al., 2005
Bivalves	Marine	PFOA	Canada: Frobisher Bay, NU	μg/kg ww	–	<0.2	–	<0.2	<0.2	Tomy et al., 2004
Bivalves	Marine	PFOS	Canada: Frobisher Bay, NU	μg/kg ww	–	0.28	–	0.08	0.6	Tomy et al., 2004
Bivalves	Marine	PFOS	Caribbean Sea: Puerto Rico	μg/kg dw	–	437	–	331	543	Kannan et al., 2002
Bivalves	Marine	PFOS	Gulf of Mexico: AL	μg/kg dw	–	325	–	<50	545	Kannan et al., 2002
Bivalves	Marine	PFOS	Gulf of Mexico: FL	μg/kg dw	–	367	–	<50	733	Kannan et al., 2002
Bivalves	Marine	PFOS	Gulf of Mexico: LA	μg/kg dw	–	291	–	<45	997	Kannan et al., 2002
Bivalves	Marine	PFOS	Gulf of Mexico: MS	μg/kg dw	–	417	–	<53	661	Kannan et al., 2002
Bivalves	Marine	PFOS	Gulf of Mexico: TX	μg/kg dw	–	406	–	<48	1,225	Kannan et al., 2002
Bivalves	Marine	PFOS	USA: Chesapeake Bay, MD	μg/kg dw	–	229	–	<43	1,106	Kannan et al., 2002
Bivalves	Marine	PFOS	USA: Chesapeake Bay, VA	μg/kg dw	–	<50	–	<45	<67	Kannan et al., 2002
Crustacean	Freshwater	PFOA	USA: Calumet River, MI	μg/kg ww	–	–	–	<5	<5	Kannan et al., 2005
Crustacean	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<5	<5	Kannan et al., 2005
Crustacean	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<5	<5	Kannan et al., 2005
Crustacean	Freshwater	PFOA	USA: Calumet River, MI	μg/kg ww	–	–	–	<0.2	<0.2	Kannan et al., 2005
Crustacean	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<0.2	<0.2	Kannan et al., 2005
Crustacean	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<0.2	<0.2	Kannan et al., 2005
Crustacean	Freshwater	PFOS	USA: Calumet River, MI	μg/kg ww	–	–	–	<2	<2	Kannan et al., 2005
Crustacean	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	2.9	2.9	Kannan et al., 2005
Crustacean	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	<2	<2	Kannan et al., 2005
Crustacean	Freshwater	PFOS	USA: Calumet River, MI	μg/kg ww	–	–	–	3.7	3.7	Kannan et al., 2005
Crustacean	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	4.3	4.3	Kannan et al., 2005
Crustacean	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	2.4	2.4	Kannan et al., 2005
Crustacean	Marine	PFOA	Canada: Davis Strait, NU	μg/kg ww	–	0.17	–	<0.2	0.5	Tomy et al., 2004
Crustacean	Marine	PFOS	Canada: Davis Strait, NU	μg/kg ww	–	0.35	–	<0.06	0.9	Tomy et al., 2004
Fish muscle	Freshwater	PFOA	USA: Calumet River, MI	μg/kg ww	–	–	–	<0.2	<2	Kannan et al., 2005
Fish muscle	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<2	<2	Kannan et al., 2005
Fish muscle	Freshwater	PFOA	USA: Raisin River, MI	μg/kg ww	–	–	–	<2	<2	Kannan et al., 2005

(*continued*)

EXHIBIT 23 (Continued)

Medium	Habitat	Analyte	Location	Units	Geometric mean	Arithmetic mean	Median	Minimum	Maximum	Citation
Fish muscle	Freshwater	PFOS	USA: Calumet River, MI	μg/kg ww	–	–	–	2.5	7.6	Kannan et al., 2005
Fish muscle	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	2	41	Kannan et al., 2005
Fish muscle	Freshwater	PFOS	USA: Raisin River, MI	μg/kg ww	–	–	–	<2	2.7	Kannan et al., 2005
Fish muscle	Freshwater	PFOS	USA: Great Lakes	μg/kg ww	–	–	–	–	296	RPA & BRE Environment, 2004
Fish muscle	Freshwater	PFOS	USA: MI	μg/kg ww	–	–	–	<7	297	Sinclair et al., 2004
Fish muscle	Unknown	PFOS	USA	μg/kg ww	–	–	–	–	923	RPA & BRE Environment, 2004
Fish muscle	Freshwater	PFOS	USA: Bossier City, LA	μg/kg ww	56	108	–	5	522	Lanza, 2015
Fish heart	Freshwater	PFOS	USA: Bossier City, LA	μg/kg ww	813	1,082	–	279	1,824	Lanza, 2015
Fish gill	Freshwater	PFOS	USA: Bossier City, LA	μg/kg ww	94	158	–	16	522	Lanza, 2015
Fish gonad	Freshwater	PFOS	USA: Bossier City, LA	μg/kg ww	392	604	–	58	1,666	Lanza, 2015
Fish digestive tract	Freshwater	PFOS	USA: Bossier City, LA	μg/kg ww	131	189	–	30	694	Lanza, 2015
Fish eggs	Freshwater	PFOS	USA: Great Lakes	μg/kg ww	–	–	–	–	250	Giesy & Kannan, 2002

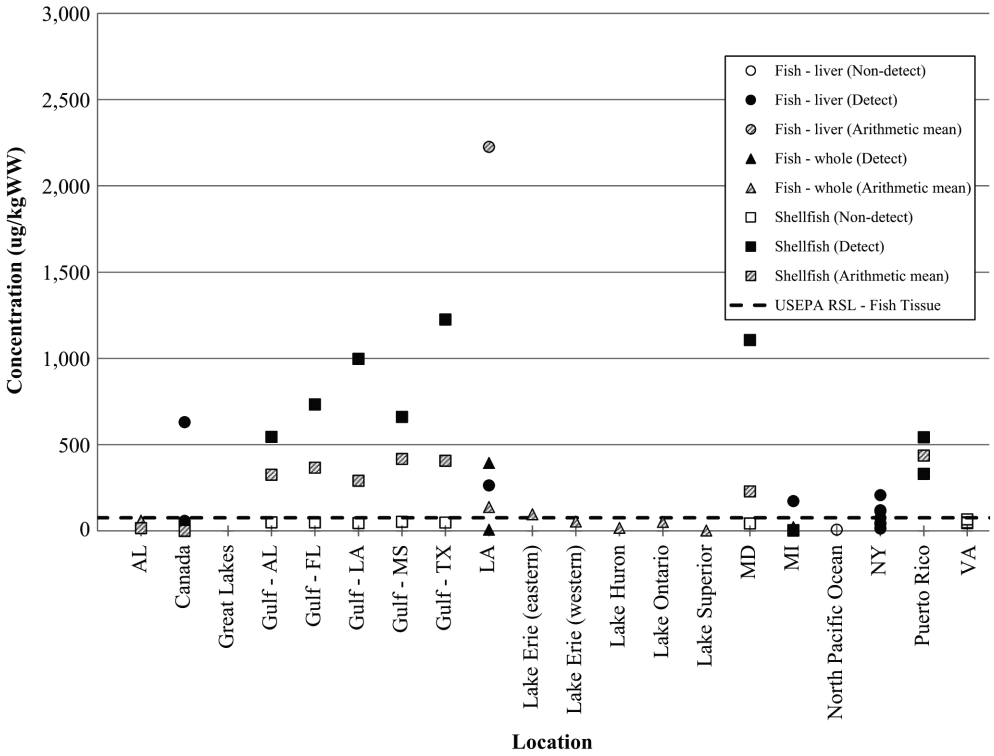


EXHIBIT 24 Locations in the United States and Canada with human tissue background data for PFOA: whole blood, serum, umbilical cord blood, plasma

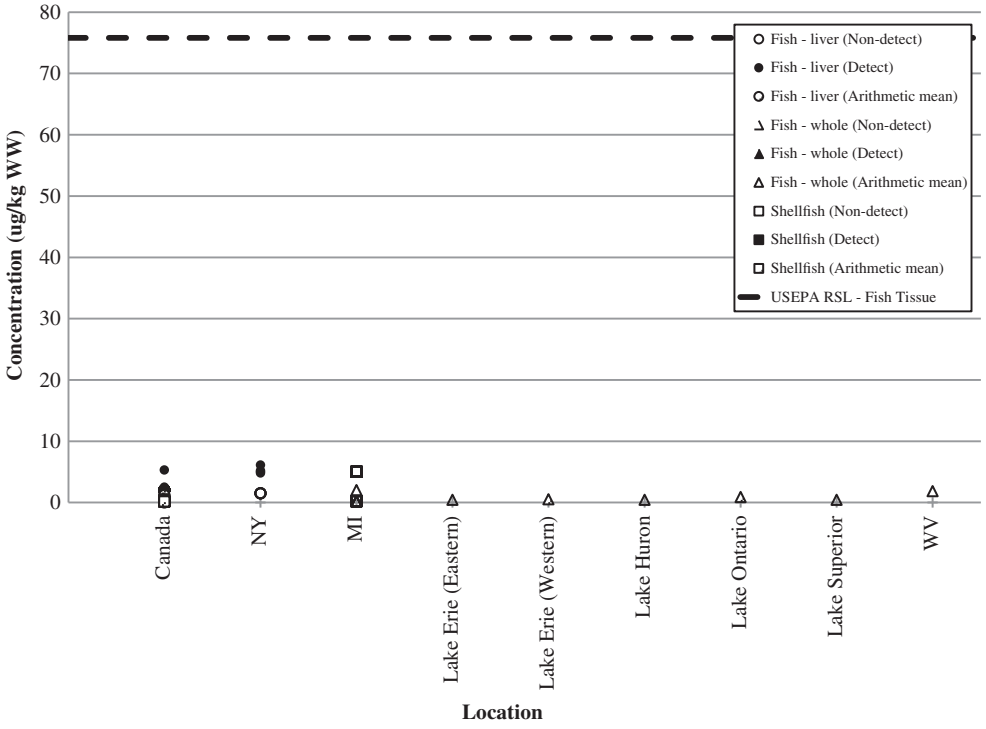


EXHIBIT 25 Scatter plot of fish and shellfish background data for PFOS

EXHIBIT 26 Scatter plot of fish and shellfish background data for PFOA

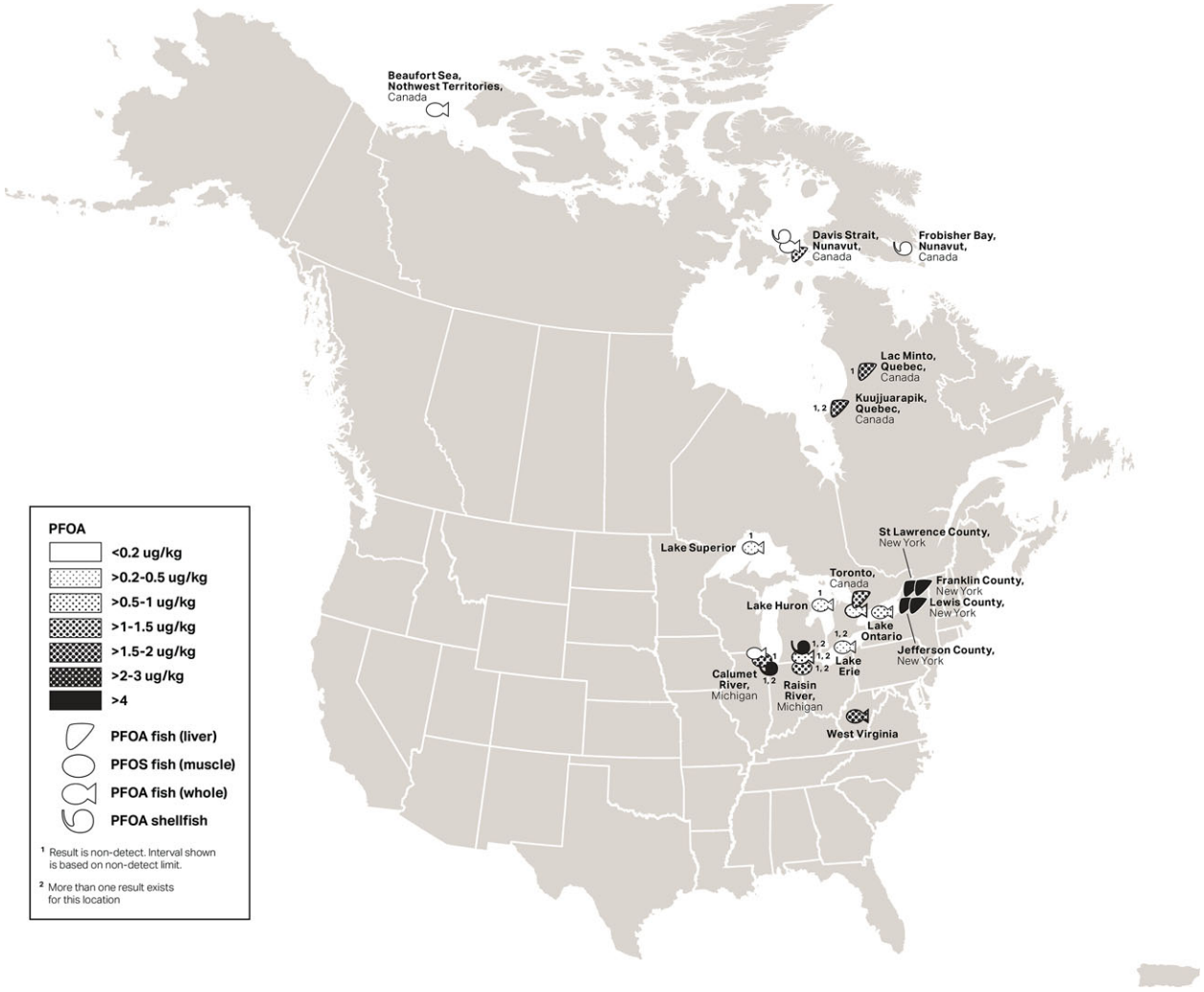


EXHIBIT 27 Locations in the United States and Canada with fish and shellfish tissue background data for PFOS and PFOA

study provided a single background soil data point from 31 spatially distinct locations throughout the United States and Canada. The background dataset for soil is not particularly robust in terms of the number of samples per geographic area, but the manner in which the Rankin et al. (2016) study was conducted lends confidence to the assumption that the data do represent background levels of PFAS in soil. The available data for soil provides a general understanding of regional background concentrations and could be used informally to distinguish between potentially impacted and unimpacted areas. Site-specific soil data would be needed for a more quantitative and definitive evaluation for purposes of site characterization.

Not many conclusions can be drawn from the few freshwater sediment samples available. Sediment studies would need to be conducted on a site by site basis to develop a PFAS background dataset that could be used with adequate confidence.

Of the biotic media evaluated in this study (i.e., human blood, fish, and shellfish tissue), the most background data were identified for human blood serum, followed by fish tissue (freshwater). It was sometimes challenging to verify that concentrations of PFAS detected in blood serum from unexposed individuals actually reflect background levels.

Although background blood serum data for PFAS are more abundant than for any other tissues, the higher variability in these data on a broad scale introduces uncertainty in applying these data on a local scale. However, the background dataset gathered for blood serum can be used as a general guide with recognition of the potential influences of unrecognized exposure sources.

Similar to surface water, background data for fin fish are comprised of freshwater species collected primarily from the Great Lakes region, with only a few data points identified for marine fish species. The background data for shellfish reflect marine species collected from the Gulf of Mexico, Caribbean, and two locations on the eastern U.S. coast. Only a few data points were identified for freshwater crustaceans and bivalves, which were mainly collected from riverine systems in Michigan.

The very localized background datasets for fish and shellfish preclude a robust evaluation of background conditions on a broad scale. The limited number of samples and wide variability in these small datasets also introduce an uncertainty in the development of regional background levels, and the lack of data from other parts of the United States and Canada represents an important data gap. Fish tissue studies would need to be conducted on a site by site basis

to develop background datasets that could be used with adequate confidence.

The available background data presented in the scatter plots for soil and sediment, surface water, drinking water, human blood serum, and fish and shellfish tissue provide insight into the specific media for which health advisory levels or other risk-based screening levels may be below background levels. Applying health advisory levels that are below site-specific background concentrations should be avoided or at least considered in remedial project decision-making so that cleanup goals are not set below background. Of the media evaluated, only soil and sediment background PFOS data were consistently reported below USEPA residential RSL. Whereas, PFOS detections in surface water and fish tissue often exceed the respective health advisory levels. Data reported for drinking water demonstrate geometric mean PFAS concentrations well below the health advisory level, but exceedances of individual data points occur. Data reported for PFOS in human blood serum demonstrate maximum and mean (geometric and arithmetic) concentrations above those observed among the general population as defined as the 95th percentile from the CDC's NHANES (2011–2012) dataset.

Overall, this compilation of publicly available data representing ambient or background levels of PFOA and PFOS in multiple media provides an assessment of the current state of knowledge at a national level and points out the potential for overestimation of site-related contributions in conceptual site model development, site characterization, risk assessment, and, ultimately, in undertaking remediation decisions. Site investigation strategies should include a goal of understanding background levels to assist in a more robust definition of site-related contributions, especially in urbanized or industrialized areas. Remedial action goals and remedial effectiveness monitoring at individual sites also need to take site-specific background levels into consideration, since remediation to levels below background would generally be considered infeasible and unnecessary. Regulatory approaches that consider the ubiquitous nature of PFAS distribution may also be necessary, similar to approaches developed for PAHs (DTSC, 2009). Case studies where PFAS background levels were considered are currently under development at several sites but have not yet been published.

In summary, more studies are needed to better understand background concentrations of PFAS in the environment. Data gathered as part of this evaluation provide an overview of the type, quantity, and quality of data currently available. PFAS data of this nature are continuously being published and should be considered in supplement to the data presented in this report. For most media, site-specific background data, representing upstream, upgradient, or reference areas should be collected at sites with potential impacts from PFAS for the benefit of site characterization and remediation efforts.

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Research Paper

Vermont-wide assessment of anthropogenic background concentrations of perfluoroalkyl substances in surface soils

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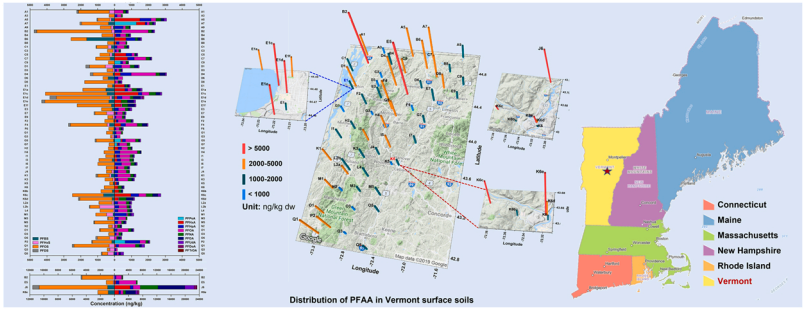
HIGHLIGHTS

- Anthropogenic background concentrations of PFAA were monitored in 66 shallow surface soils.
- Total PFAA concentrations ranged from 540 to 36,000 ng/kg dry soil weight.
- PFOS was the most dominant substance followed by PFNA and PFOA in all soil samples.
- Higher total PFAA levels were detected in northern parts of Vermont.
- PFAA levels were correlated positively with human activities and negatively with natural ones.

GRAPHICAL ABSTRACT



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ABSTRACT

Shallow surface soils from 66 suburban sampling locations across Vermont were analyzed for 17 different perfluoroalkyl acids (PFAA). PFAA were detected in all 66 surface soils, with a total concentration of PFAA ranging from 540 to 36,000 ng/kg dry soil weight (dw). Despite the complexity of site-specific factors, some general trends and correlations in PFAA concentrations were observed. For instance, perfluoro-1-octanesulfonate (PFOS) dominated in all soil samples while seven other PFAA, including perfluoro-n-nonanoic acid, perfluoro-n-octanoic acid, perfluoro-n-hexanoic acid, perfluoro-n-heptanoic acid, perfluoro-n-decanoic acid, perfluoro-n-undecanoic acid, perfluoro-1-butanesulfonate, and perfluoro-1-hexanesulfonate (PFNA, PFOA, PFHxA, PFHpA, PFDA, PFUnDA, and PFBS, respectively), were identified at more than 50 % of the locations. Perfluoroalkyl carboxylic acids (PFCA) showed a positive correlation with total organic carbon, whereas no clear correlation was observed for perfluoroalkyl sulfonate acids (PFSA). In addition, variations in geographical distributions of PFAA were observed, with relatively higher total PFAA in northern regions when compared to Southern Vermont. Moreover, PFHxA, PFNA, PFDA, PFUnDA, PFOS, and total PFAA were positively correlated to land-use types in Northern Vermont. These results are useful for understanding unique behaviors of PFCA vs. PFSA in geospatially distributed surface soils and for providing anthropogenic background data for setting PFAS cleanup standards for surface soils.

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1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a diverse group of anthropogenic organic substances containing the perfluoro moiety (C_nF_{2n+1}), which confers unique hydrophobic and lipophobic (stain-resistant) and surfactant properties that make them thermally and chemically stable (Muller and Yingling, 2020b; Buck et al., 2011). Since the 1950s, such properties have led to extensive PFAS application in various industrial and commercial products, including surfactants, refrigerants, lubricants, paints, aqueous film-forming foams (AFFFs), textile coatings, cosmetics, and food packaging (Houtz et al., 2013; Prevedouros et al., 2006; Fujii et al., 2007). Consequently, PFAS can be released into the environment via different pathways, including production, application, transport, disposal of related products, and degradation from precursors (Muller and Yingling, 2020a; Sznajder--Katarzyńska et al., 2019). Recently, numerous studies have reported that PFAS are ubiquitous in various environmental compartments, including air, water, soil, and wastewater sludge, due to their large-scale and long-term usage all over the world (Crone et al., 2019; Lai et al., 2019; Yu et al., 2020; Rankin et al., 2016; Kaboré et al., 2018; Cui et al., 2020; Barisci and Suri, 2021; Cai et al., 2022). More importantly, studies have shown that PFAS are environmentally persistent and bio-accumulative, therefore, they can be taken up by organisms and biomagnified through the food chain to wildlife and humans (Hori et al., 2004; Haukås et al., 2007; Lam et al., 2014; Teunen et al., 2021; Semerád et al., 2022). Thus, PFAS have attracted increasing international concern for human health and the environment as contaminants of emerging concern due to their environmental persistency, bioaccumulation, widespread distribution, and potential toxicity (Fujii et al., 2007; Qi et al., 2016; Wei et al., 2018; Sunderland et al., 2019; Fenton et al., 2021; Li et al., 2015).

Generally, PFAS can be released to the environment from direct sources, such as manufacturing, use, and disposal of PFAS, and indirectly via the transformation of precursor substances in the environment (Buck et al., 2011; Li et al., 2015; Eriksson et al., 2017; Garg et al., 2020; Langberg et al., 2021). Recently, the pollution caused by PFAS in the aquatic environment has been widely investigated and documented (Clara et al., 2009; Möller et al., 2010; McMahon et al., 2022; Podder et al., 2021), however, the studies focusing on the background occurrence and distribution of PFAS in soils are still scarce (Li et al., 2010a). As one of the common destinations of PFAS in the environment, soils can be polluted by PFAS via different routes, including point-source pollution, atmospheric bulk deposition, land application of biosolids, and surface runoff (Rauert et al., 2018; Kim and Kannan, 2007; Venkatesan and Halden, 2013). PFAS can also be transferred from soils to atmosphere, surface water, and groundwater via volatilization, diffusion, leaching, and mass flow (Meng et al., 2015; Armitage et al., 2009). Further, PFAS can be introduced into the food chain from soils through soil-water-plant-animal-human pathway, which poses a potential threat to the ecosystem and human health (Scher et al., 2018; Liu et al., 2019; Ghisi et al., 2019). To date, considerable efforts have been mainly devoted to soils that are known to be impacted by firefighter training facilities, agricultural land application of sludge from wastewater treatment plants, or the manufacturing and use of perfluoro-containing products (Houtz et al., 2013; Rankin et al., 2016; Sörengård et al., 2019; Maldonado et al., 2022). Though PFAS occurrence and distribution in surface soils are of great significance, available data on the anthropogenic background concentrations and distribution of PFAS in surface soils are still scarce (Rankin et al., 2016; Strynar et al., 2012).

A database of anthropogenic background PFAS concentrations (e.g., low levels that exist in the environment due to dispersion of these chemicals) would enable researchers and the stakeholders to develop a more comprehensive understanding of PFAS pollution and fate and transport in the environment. Knowledge of background concentrations becomes crucial when delineating the boundaries of contamination attributable to known or suspected release and establishing the area where liability for cleanup exists.

In this study, we investigated the anthropogenic background concentrations of selected 17 perfluoroalkyl acids (PFAA) and their geographic distribution in the surface soils of Vermont (VT). Vermont is a primarily rural state located in the northeastern part of the United States of America (USA). Two specific subgroups of PFAA, namely perfluoroalkylcarboxylic acids (PFCA) and perfluoroalkylsufonate acids (PFSA), were studied due to their prevalence and persistence in the environment (Rankin et al., 2016; Sharma et al., 2016; Houde et al., 2006; Rayne and Forest, 2009). Instead of focusing on soils known to be polluted or potentially polluted by PFAS-related point sources (e.g., Teflon fabric-coating facility; fire-fighting training facilities), we have investigated the anthropogenic background concentrations of PFAA in surface soil samples collected from 66 locations across VT. These 66 locations were not suspected to be contaminated by local PFAA sources. Multivariate statistical methods and high-resolution land-use analysis were applied to: (1) examine spatial patterns in the distribution and composition profiles of PFAA, and (2) provide new insights into possible role of anthropogenic activities on the geographic distribution of PFAA in surface soils. For the first time, this study provides critical information about the anthropogenic background concentrations of PFAA across VT surface soils, which may aid in the development of soil standards in the near future. In addition, these data will provide an improved understanding of the behavior of PFCA and PFSA in surface soil and casual relationships between individual PFAA and soil total organic carbon (TOC), which has been shown to influence PFAS partitioning in soil (Campos Pereira et al., 2018; Hunter Anderson et al., 2019; Vierke et al., 2014). Collectively, the results from this study can assist environmental professionals in the management of PFAS soil pollution and thereby mitigate potential environmental and human health impacts.

2. Materials and methods

2.1. Sampling design, collection, and extraction

The study area was the state of VT, and a gridded approach to sample collection across the state was applied (see details in the supporting information (SI) and Fig. S1). Sample collection targeted publicly owned lands (e.g., municipal parks and greens, municipal building lawns, school lawns, and town forests), which were not close to or located at known or suspected PFAS sources such as firefighting training facilities and air base. Samples were collected from 66 locations across VT in the summer of 2018 (Fig. 1). Around 500 g of soil was collected from the top 15 cm (approximately six inches beneath any turf or detritus cover). Sampling equipment avoided the use of Teflon-containing materials, and a total of 88 field blanks and duplicate samples were collected. Detailed information about the samples, including their identity, property name, location, and sampling data, are provided in Table S1 (see SI).

PFAA were extracted from soil samples using the method developed by Rankin et al (Rankin et al., 2016). In addition, total organic carbon (TOC) and percent solids in each soil sample were determined following ASTM 2000 Method and ATSM D2216 Method, respectively. Analytical methods are detailed in the SI.

2.2. Chemicals and reagents

Thirteen PFCA standards and four PFSA standards were purchased from Wellington Laboratories Inc. (Guelph, Ontario, Canada) in a mixture named PFCA-MXB. Perfluoro-n-[$^{13}C_8$] octanoic acid ($^{13}C_8$-PFOA (M8PFOA)), a mixture of nine mass-labeled PFCA and two PFSA standards named MPFAC-MXA were purchased from Wellington Laboratories Inc. Abbreviation and purity of the native and isotopically labeled PFAA standards are provided in Table S2 (see SI).

High performance liquid chromatography (HPLC) grade methanol (≥99.9 %), acetonitrile (ACN, ≥99.9 %), and acetic acid (≥99.7 %) were purchased from Sigma-Aldrich. Sodium hydroxide (NaOH),

tetrabutylammonium hydrogen sulfate (TBAHS), and sodium carbonate (Na_2CO_3) were purchased from Aldrich Chemical (Milwaukee, WI, USA). Methyl tert-butyl ether (MTBE) was purchased from Fisher Chemical (Fairlawn, NJ, USA). Oasis HLB solid-phase extraction (SPE) cartridges, 35 cm^3 capacity, were purchased from Waters (Milford, MA, USA). Milli-Q water was generated by Milli-Q® Reference (Merck Millipore, Germany).

2.3. Instrumental analysis, quality assurance and quality control

A liquid chromatography-tandem mass spectrometry (LC-MS/MS) system was applied to detect and quantify PFAA A Shimadzu Prominence LC using a Waters Atlantis dC18 column was coupled to an ABI QTRAP 4000 mass spectrometer (Applied Biosystems, Foster City, CA, USA) in negative electrospray ionization mode. Detailed instrumental parameters are summarized in Table S3 (see SI). Quantification was based on internal standardization solvent-based calibration curves with nine-point, and the regression coefficients (r^2) were over 0.99 for every analyte. Method detection limits (MDLs) were established during validation and were determined by multiplying the standard deviation by the student's t-value of 3.143 for seven replicates. Method reporting limits (MRLs) were set at five times the MDL. MDLs and MRLs for the 17 PFAS are provided in Table S4 (see SI).

Polytertafluoroethylene (PTFE) and fluoropolymer materials were avoided throughout the study to minimize cross-contamination of the samples. Each sampling batch contained around 10–15 samples, and freshly prepared calibration standards (minimum six points) were analyzed before and after every batch. Field reagent blanks (FBs), method blanks (MBs), and laboratory control sample (LCS) were routinely included within each batch and were treated in the same way as actual samples. PFOA was detected in one of the MBs at a level below the MDL. However, the absence of quantifiable levels of PFAA in the blanks indicates that concentrations measured in the samples were attributed to the soils and no cross-contamination (see Tables S5–S6, SI). The average recovery of $^{13}C_8$-PFOA was 80.33 % (relative standard deviation, RSD: 7.62 %) and detailed QA/QC results were provided in the Tables S7–S8 (see SI).

2.4. Statistical analysis

PFAA concentrations are reported on a dry weight (dw) basis. Possible outliers of total PFAA (ΣPFAA) were determined by Dixon's outlier tests at the 5 % significance using ProUCL software v5.2 (EPA, USA). After omitting outliers, statistical analyses including descriptive statistics, principal component analysis (PCA), and Spearman's rank correlation analysis were performed by OriginPro 9.0 (OriginLab Company, USA). Statistical significance was set at a 0.05 *p*-value cutoff. During the analyses, the concentrations below MDLs were assigned values equal to half of the MDL. Land-use analysis was coupled with Spearman's rank correlation analysis to evaluate potential human activity influence on the anthropogenic background concentrations and their geographic distribution of PFAA in VT surface soils. Land-use data were obtained using ArcGIS pro (ESRI, USA). Specifically, four buffers (100 m, 250 m, 500 m, and 1000 m) associated with each sampling site were created to extract the land cover data expressed as a percentage based on 30 m land cover resolution. Fifteen unique land-use classifications were aggregated to nine groups that were later classified as Human Activities (HA) and Nature (NT). HA contains categories of Developed Intensity (DI), Residential Intensity (RI), Agriculture (AGR), and Hay. NT includes categories of Forest (FR), Wetland (WD), Water, Grassland and Shrub (GS), as well as Rock. The resulting PFAA data were further used as inputs for the ordinary Kriging interpolation method to illustrate the predicted spatial distribution of PFAA in VT surface soils using ArcGIS Pro. VT population estimates from United States Census Bureau (2015, American Community Survey (ACS)) at zip code-level were used to calculate population density (Clara et al., 2009).

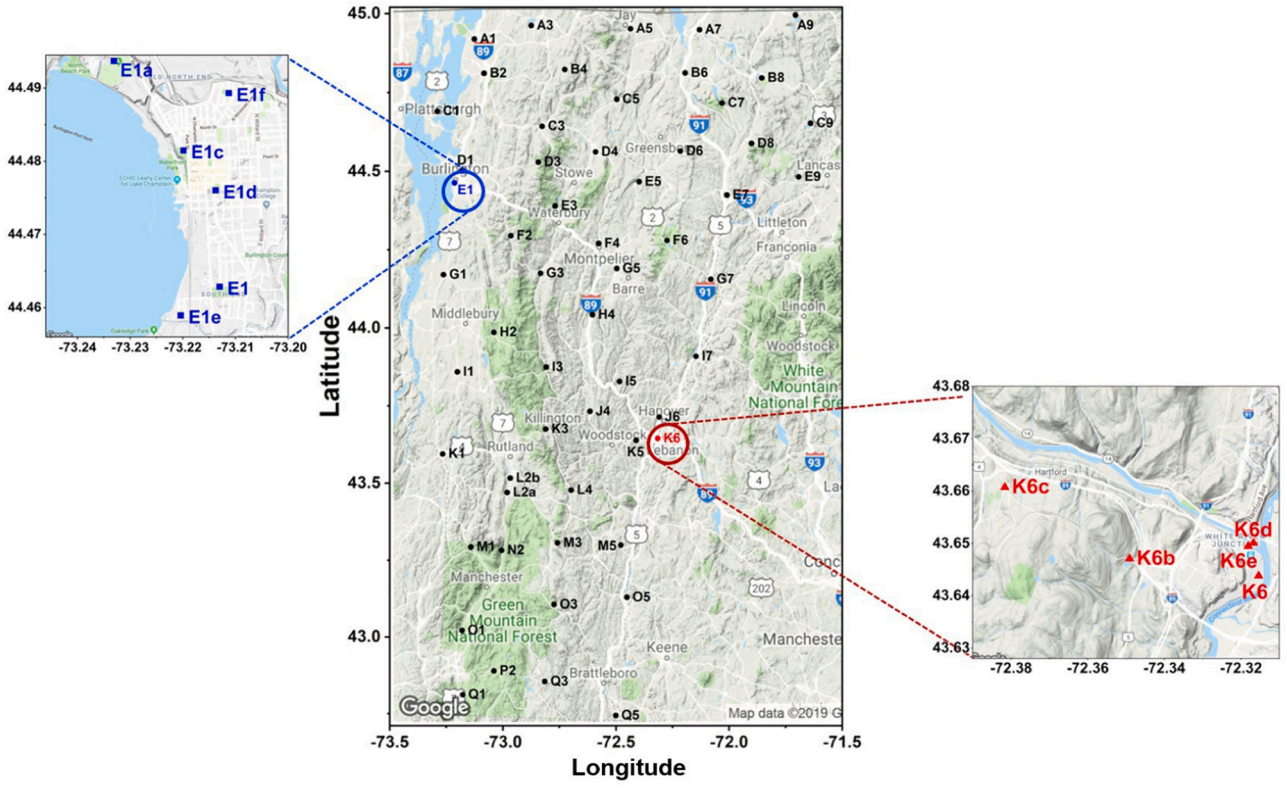

Fig. 1. Map of sampling sites in the state of VT. The left-hand figure shows the higher-density sampling sites in the Burlington area. The right-hand figure shows the higher-density sampling sites in the White River Junction area.

3. Results and discussion

3.1. Composition and distribution patterns of PFAA in VT surface soils

The background concentrations of PFAA and their relative abundance are depicted in Fig. 2(a) and (b), respectively.

PFAA were found to be ubiquitous in surface soils, with at least some compounds detected in samples from all 66 locations across VT. Six PFCAs (PFHxA, PFHpA, PFOA, PFNA, PFDA, and PFUndA) and four PFSAs (PFBS, PFHxS, PFOS, and PFDS) were detected (see Table S2 for

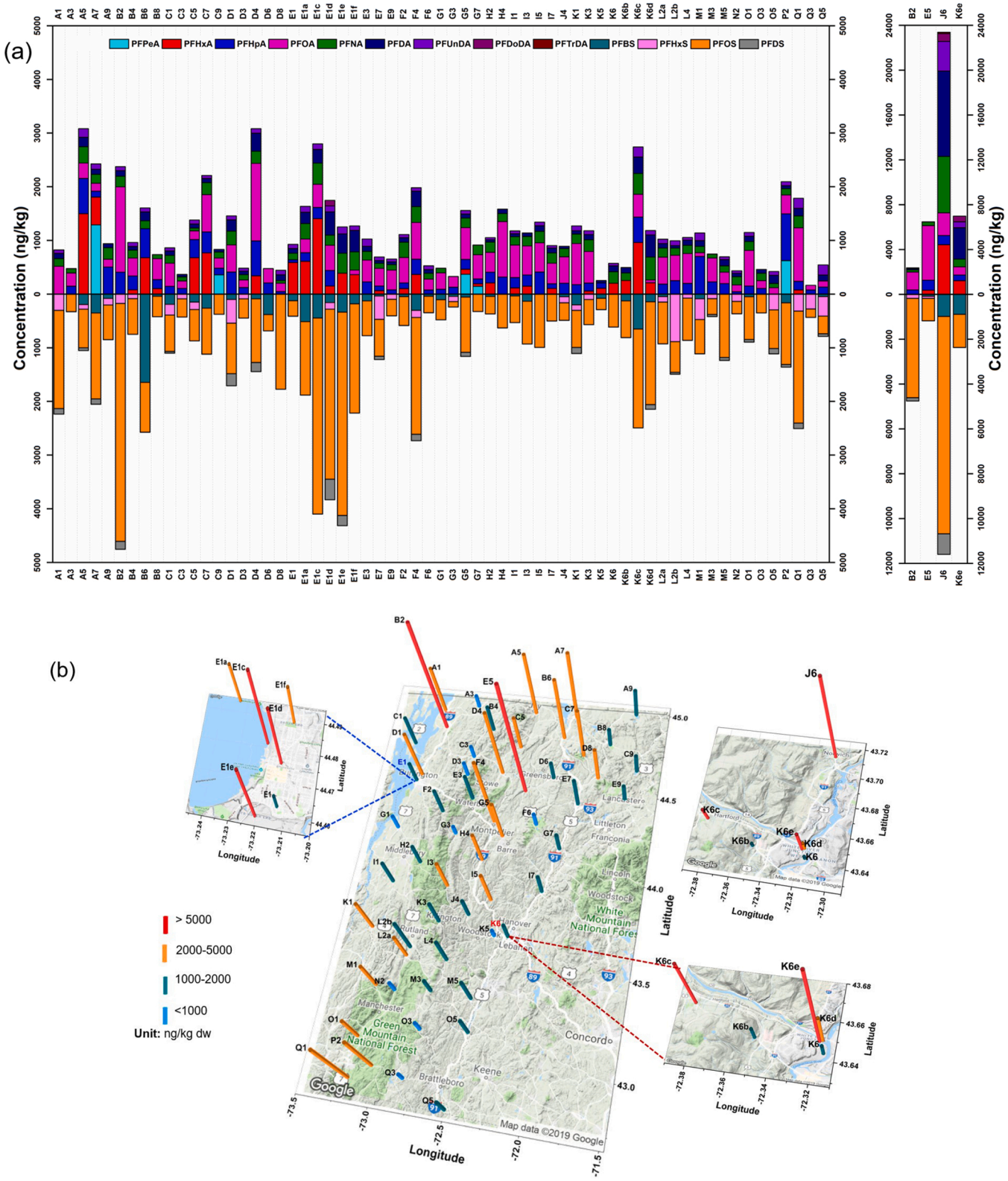

Fig. 2. Concentrations of detected PFAA (ng/kg) species (a) including subgroups of six PFCAs (upward-directed bars) and four PFSAs (downward-directed bars); and the geographical distribution and abundance of ΣPFAA in VT surface soils (b).

abbreviations) at frequencies higher than 30 % (Table S8). PFOS was detected in all soil samples, followed by PFNA (92 %), PFOA (91 %), PFHpA (89 %), PFDA (86 %), PFUnDA (73 %), PFBS (63 %), PFHxDA (50 %), PFHxS (44 %), and PFDS (35 %). PFBA was not found in any soil sample, while PFPeA, PFDoDA, PFTrDA, PFTeDA, PFHxDA, and PFODA were rarely observed at quantifiable levels (<10 %). Therefore, these seven PFAA were excluded from further analysis beyond descriptive statistics.

Nine out of 17 PFAA showed detection frequency of >40 %, and their concentrations ranged over two orders-of-magnitude (Fig. 3). Except PFOS, the 95th percentiles of individual PFAA were more significant, higher than 100 ng/kg but less than 1000 ng/kg. For the two dominant species, PFOA and PFOS, their median concentrations were in the range of 300–800 ng/kg.

The levels of PFAA in VT soils were highly variable among locations (Fig. 2(b) and Table S9). The total concentration of quantifiable PFAA (∑PFAA) ranged from 540 to 36,000 ng/kg, with a geometric mean of 2100 ng/kg. The subgroup total PFCA (∑PFCA) ranged from 160 to 23,000 ng/kg, with a geometric mean of 1100 ng/kg, while total PFSA (∑PFSA) varied from 240 to12,000 ng/kg with a geometric mean of 960 ng/kg. The lowest ΣPFAA (540 ng/kg) was obtained in site K5 (Quechee State Park). Across VT, ΣPFAA levels higher than 5000 ng/kg were observed in eight locations, including three locations in the Burlington area (E1c, E1d, and E1e), three in the Hartford area (J6, K6e and K6c), and one near St. Albans (B2).

An exceptionally high total ∑PFAA concentration (36,000 ng/kg) was observed at location J6 (Norwich Green), of which the ∑PFCA and ∑PFSA were 23,000 ng/kg and 12,000 ng/kg, respectively. Site K6e (Veterans Memorial Park-Hartford) showed the second-highest ∑PFAA (9400 ng/kg), followed by site E5 (7700 ng/kg). These data (sites J6, K6e, and E5) were identified as outliers by ProUCL v5.2. High levels of ∑PFAA may be caused by unknown localized sources in the vicinity of these sampling sites. These three data points were omitted from the statistical analyses to avoid potential bias.

Though available studies focusing on existence of PFAA in "background" surface soils are limited, the ∑PFCA levels observed in most locations (n = 63) in VT surface soils are consistent with the global survey conducted by Rankin et al. in 2016 (Rankin et al., 2016), who showed that ∑PFCA in North America background surface soils ranged from 145 to 6080 ng/kg. Interestingly, higher ∑PFSA levels were observed in 31 locations across VT compared to the range of 35–1990 ng/kg reported by Rankin et al., 2016 (Rankin et al., 2016). Recently, Sörengård et al. investigated the spatial distribution of 28 PFAS in 27 background forest soils across Sweden and found at least three to 16 PFAS at all sampling sites with a ∑PFAS ranging from 400 to 6600 ng/kg dw (Sörengård et al., 2022). These findings are consistent with the ∑PFAA levels observed in our study. It is worth noting that quantifiable concentrations of PFAS were detected in all surface soil samples in Rankin et al., Sörengård et al. as well as in our study. Further, Strynar et al. showed the occurrence of 13 PFAA in 58.3 % surface soil samples (60 samples with 10 samples per country, including USA); the ten highest ∑PFAA detected ranged from 7810 to 129,000 ng/kg dw (Strynar et al., 2012). Interestingly, all soil samples from USA were found to contain measurable ∑PFAA and seven of them were among the ten samples with higher ∑PFAA levels. On the contrary, low or no measurable ∑PFAA were detected in >50 % samples from other countries including Greece and China (Strynar et al., 2012). Although Strynar et al. reported that PFAA were not quantitatively detected in more than 50 % soil samples from China, the Ma et al. study showed the occurrence of 17 PFAS in 171 topsoil (0–20 cm) samples, with ∑PFAS ranged from 210 to 5350 ng/kg dw, collected from sites regarded as background or residential areas without any potential PFAS point sources in Tianjin, China (Ma et al., 2022). It is worth noting that ∑PFAS levels in background surface soils may vary significantly due to differences in sampling sites, detection methods, and number of PFAS studied. Brusseau et al. study summarized the ∑PFAS levels in "background" soils reported by various studies, wherein ∑PFAS levels typically ranged from < 1–237,000 ng/kg dw (Brusseau et al., 2020). Nevertheless, by comparing the PFAS levels in "background" soils with contaminated soils using data from published studies, Brusseau et al. found that PFAS levels at contaminated sites are usually an order-of-magnitude higher than those detected in the "background" soils (Brusseau et al., 2020).

As shown in Fig. 4, the PFCA sub-group accounted for more than 50 % of ∑PFAA in soil samples collected from 41 locations, with the highest PFCA percentage (84.6 %) was found at location E5 (Buck Lake WMA). PFOS, PFNA, and PFOA were the three predominant species in most soil samples, accounting for more than 40 % of ∑PFAA at 56 locations. PFOS was the most abundant PFAA compound in VT background surface soils, accounting for around 13–18 % of ∑PFAA in the surface soils. Similarly, Strynar et al. observed that PFOS was most frequently (48 %) detected with a highest concentration of 10,100 ng/kg dw in surface soils, followed by PFOA (28 % frequency) with a highest concentration of 31,700 ng/kg dw (Strynar et al., 2012). Further, Sörengård et al. discovered that PFOS was the most frequently detected species across Sweden (Sörengård et al., 2022). However, a few studies reported PFOA as the dominant species in the background surface soils. For instance, Ma et al. observed that PFOA was the dominant species accounted for 34–48 % of ∑PFAS in surface soils without known PFAS contamination in Tianjin, China (Ma et al., 2022). Though only

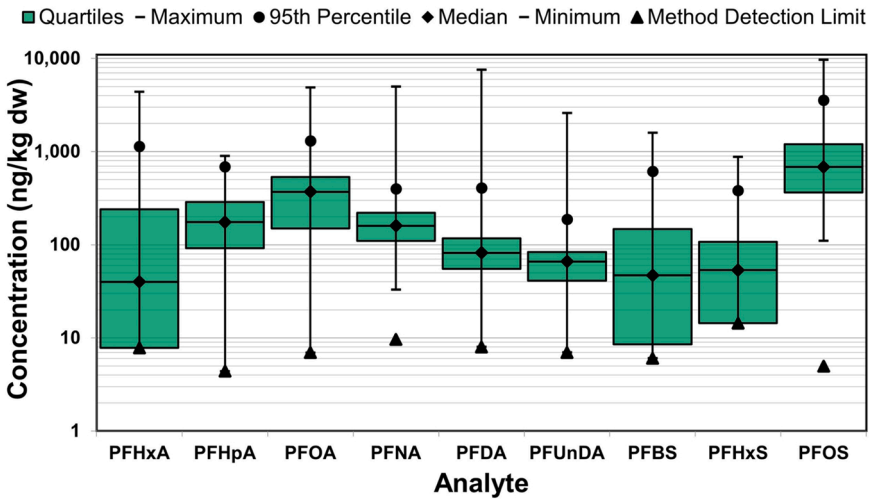

Fig. 3. The box and whisker plot for the select PFAA with greater than 40 % detection frequency at 66 sampling location.

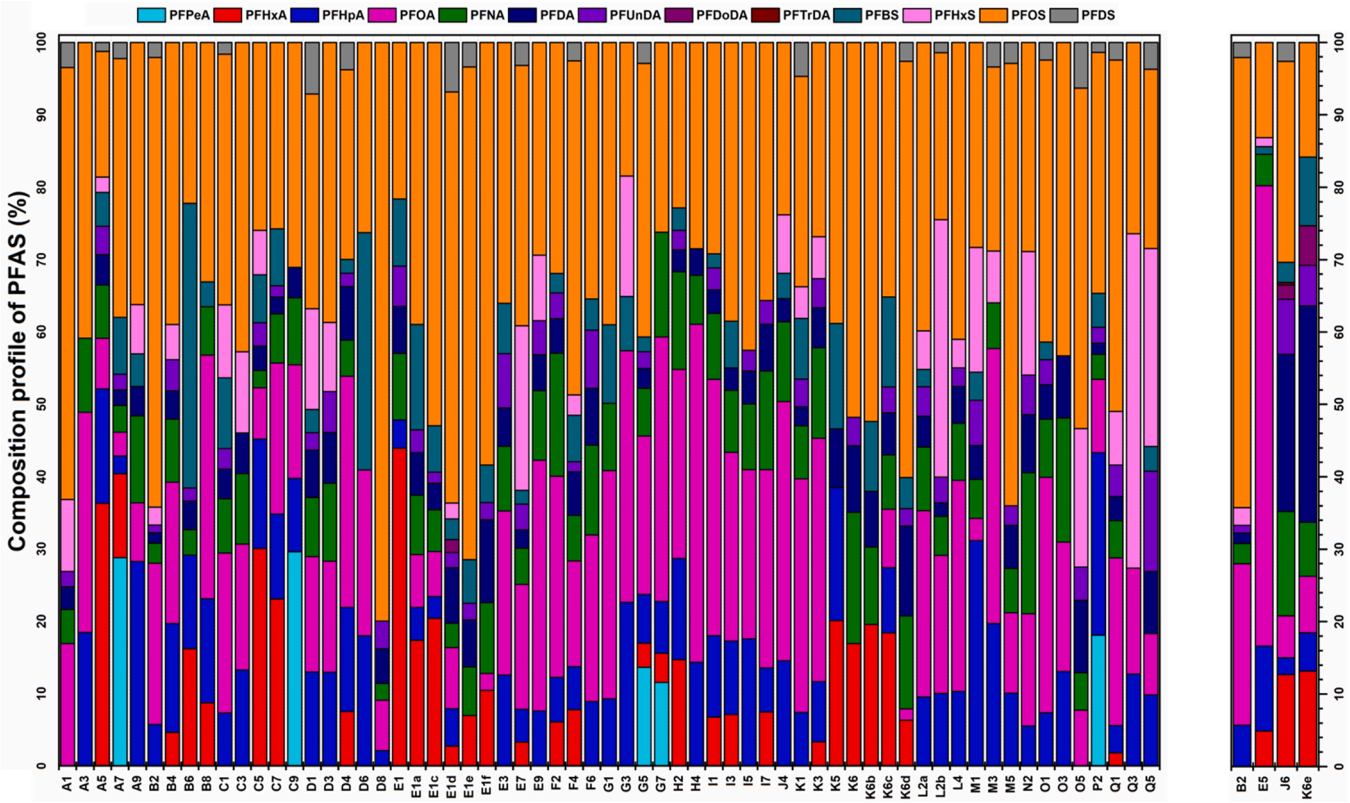

Fig. 4. Composition profiles based on quantitively detected PFAA in VT surface soils.

levels of PFOA and PFOS were studied in 28 Chinese natural mountain forest sites far away from cities and industrial plants, Wang et al. found that PFOA was more frequently detected (67 %) with concentration ranged from < 0.9–9.0 ng/kg dw compared to PFOS, which was only detected at two sites (4 % frequency) (Wang et al., 2018). Findings may vary among studies, but it is important to point out that both PFOS and PFOA are more prevalent species in surface soils without known or suspected PFAS contamination. Brusseau et al. also compared the maximum reported concentrations of PFOA and PFOS between background and contaminated soil samples, and found that PFOS maximum reported concentrations in contaminated soils were dramatically higher than those detected in background soils; for instance, the highest PFOS level detected from U.S. Air Force AFFF Impacted-Site was 460, 000 μg/kg (Brusseau et al., 2020).

3.2. Relationships with TOC and total solids content

No clear relationship between PFAA and total solids content was observed in VT surface soils. It has been widely reported that the existence of hydrophobic organic pollutants in soils can be affected by soil characteristics such as TOC (Ukalska-Jaruga et al., 2019; Nam et al., 2008). Some studies showed a positive correlation between the levels of PFAS and TOC in soils (Ma et al., 2022; Cao et al., 2019). To test this relationship, PFAA levels and TOC content (see Table S9) were investigated using Spearman's rank correlation analysis. In areas A to E (see Fig. S1), PFOA ($r = 0.617$), PFHpA ($r = 0.462$), and $\sum$PFCA ($r = 0.384$) were found to positively, but relatively weakly, correlate with soil TOC, indicating the content of TOC may be a factor affecting the distribution of PFOA, PFHpA, and $\sum$PFCA in surface soils from northern parts of VT (Areas A to E; see Fig. S1). However, in areas F-Q (Fig. S1), only PFOA ($r = 0.485$) showed a positive correlation with TOC in southern parts of VT. Thus, PFOA and PFHpA are more likely to interact with TOC compared to PFSA and other PFCA compounds, indicating that the influence of soil TOC may be specific to certain PFAA types. However, the lack of strong correlation between soil TOC and other PFAA suggests that TOC may not be a key parameter explaining the occurrence of PFAA in VT surface soils. Similar results have been reported by Wang et al. wherein the occurrence of PFOA was not significantly related to TOC of forest surface soils (Wang et al., 2018). Li et al. also reported that occurrence of PFAA in soils and sediments showed no dependence on TOC content (Li et al., 2010b). Interestingly, by studying the adsorption of PFAA on soils, Li et al. discovered that content of soil proteins, rather than TOC, may be a more important factor controlling PFAA sorption onto soils (Li et al., 2019). The reported conflicting results may suggest that PFAS concentrations may be influenced by many other unknown/undefined parameters of the soil as well as surrounding environment which requires further studies.

3.3. Geographical distribution of PFAA in VT surface soils

Fig. 2(a) indicates an uneven distribution of PFAA in surface soils across VT. To understand geographical influences, all sampling locations were divided into nine groups according to the VT biophysical regions differentiated by elevation, climate, geology, topography, hydrology, land-use history, and vegetation (Fig. 5(a)). Champlain Valley (CV), Champlain Hills (CH), Northeastern Highlands (NEH), Northern Green Mountains (NGM), Northern Vermont Piedmont (NVP), Southern Green Mountains (SGM), Southern Vermont Piedmont (SVP), Taconic Mountains (TM) and Vermont Valley (VV) in the South. Here, CV and CH were grouped together as only one sample (A3) was obtained from CH area. Similarly, TM and VV were clustered in one group as only two samples were collected from the TM area. Overall, the geographic distribution characteristics of $\sum$PFAA in VT soils were Northern VT > Southern VT, Western VT > Eastern VT, and geographically Valleys > Piedmonts > Mountains. Specifically, the geometric means of $\sum$PFAA decreased in the following order: CV+CH > NVP > TM+VV > NGM > NEH > SVP > SGM (Fig. 5(b)).

To further investigate the geographical differences of PFAA

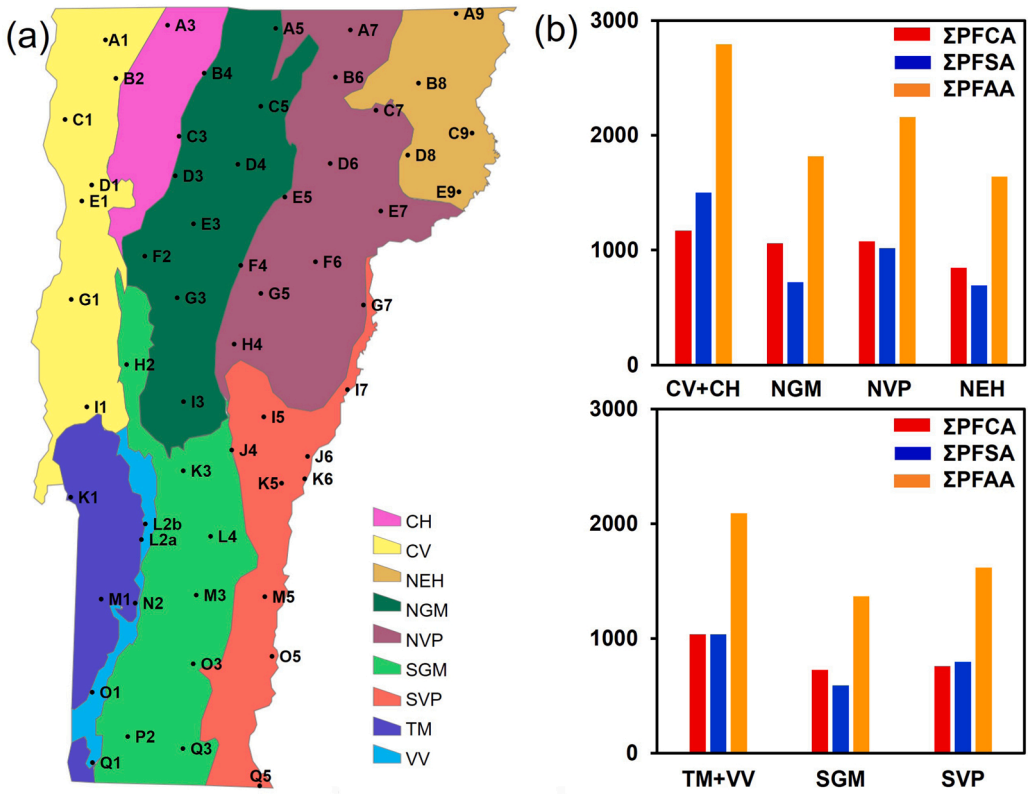

Fig. 5. The biophysical regions of Vermont (a); Geometric means of each biophysical region (b). Acronyms: CV-Champlain Valley; NEH- Northeastern Highlands; NGM- Northern Green Mountains; NVP- Northern Vermont Piedmont in the North; SGM- Southern Green Mountains; SVP- Southern Vermont Piedmont; TM- Taconic Mountains; and VV- Vermont Valley in the South.

distribution in VT surface soils, PCA analysis was utilized to explore the similarities and differences among samples from different regions. SGM, SVP, and TM+VV were treated as one group named SO for the PCA analysis. As illustrated in Fig. 6 and Table S10, principal component 1 (PC1) explained 73.8 % of the total variance, of which PFOS contributed most to PC1. This is consistent with the PFAA profile, where PFOS is the predominant species in most sampling sites. PC2 contributed 11.4 %, with the highest loading factors from PFOA, PFHxA, and PFBS. Though most sites presented no notable differences in PFAA patterns as shown in the circle, partial separation of the locations was found. Specifically,

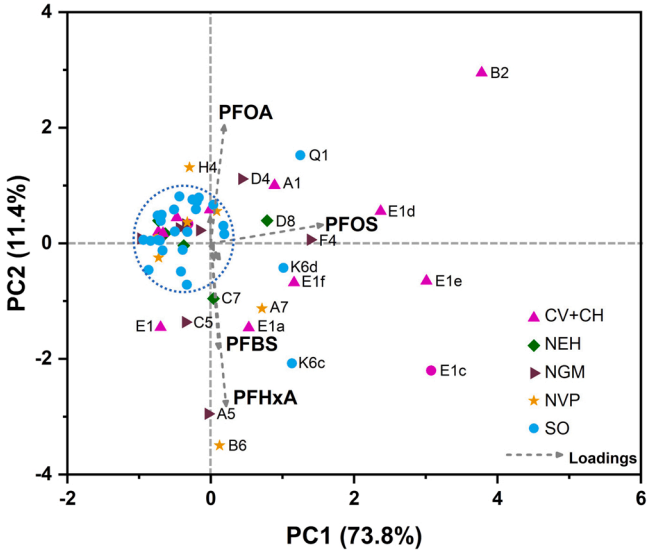

Fig. 6. PCA score plot and loading plot for PFAA in VT surface soils.

sites that fell outside the cluster included A1, B2, E1, E1a, E1c, E1d, E1e, and E1f from the CV area; Q1 from the TM+VV area; D4, F4, A5, C5 from the NGM area; C7 and D8 from the NEH area; B6, A7 and H4 from the NVP area; and K6b, K6d from the SVP area. In general, most of these "outliers" showed higher ∑PFAA levels than those in the central cluster.

3.4. PFAA in relation to land-use

PCA result elucidates an uneven distribution of PFAA in VT surface soils with significant regional differences and isolated contamination "hot-spots". Many studies reported the occurrence of organic contaminants, such as polycyclic aromatic hydrocarbons (PAHs), antibiotics, and PFAS, can be strongly related to geographic information including population density and land-use types (Chen et al., 2018; Li et al., 2016; Zushi et al., 2012; Zushi and Masunaga, 2011). Similarly, our results imply that the geographical conditions may affect PFAA distribution in VT soils. Though samples were collected from properties supposed to be unaffected by local PFAS sources, the occurrence of PFAA in surface soils could be influenced by adjacent human-related activities, perhaps indicating a better need to understand local sources of PFAA.

VT is a primarily rural state, and most areas have relatively low population density. Population density at zip code level was mapped as displayed in Fig. S2 to work as an indicator of local anthropogenic influences. Not surprisingly, most samples (except E5 and J6) with ΣPFAA levels higher than 5000 ng/kg were collected from areas with relatively higher population densities greater than 100/km^2. Specifically, E1c, E1d, E1e were obtained from Burlington area in CV region, which has the highest population density in VT. In the case of samples with ΣPFAA levels higher than 2000 ng/kg, most samples (except E5, A5, C7, D8, and P2) were collected from areas with a population density higher than 25/km^2. On the contrary, less ΣPFAA were detected in areas with lower population densities such as A9 and C9. Such phenomena suggest that

locally derived PFAA in densely populated areas might have contributed to the levels of ΣPFAA in their neighborhoods.

In addition to population density, land-use data is applied to (1) explore possible correlations between land-use characteristics and soil PFAA distribution and (2) seek information relating PFAA sources to specific land-use types. To investigate land use, circular buffers centered at each sampling site were established with four radii ranging from 100 m to 1000 m, and the area occupied by each land-use category (see Section 2.5) within each buffer was determined. Results are summarized in the SI Tables S11–S14. Based on the result of PCA analysis, VT was divided into two regions for the land-use analysis: Northern VT (CV, CH, NGM, NVP, and NEH) and Southern VT (TM, VV, SGM, and SVP). Spearman's rank correlation analysis was performed to assess the influence of land-use types on ∑PFAA, ∑PFCA, and ∑PFSA in the two regions, and the detailed results were given in Table 1 and Table S15, respectively. As Agriculture, Rock, Hay, and Water were found to have a neglectable impact on PFAA occurrence, these land-use types would not be further discussed in this study.

In Northern VT (Table 1), the levels of ΣPFAA in surface soils were found to be positively related to land-use types under the group of human activities (HA%) and negatively related to land-use types under nature (NA%) at all spatial scales ($p < 0.05$). More importantly, improved correlations between ΣPFAA levels and land-use types were observed with increased spatial scales, suggesting that land-use patterns affect ΣPFAA at larger spatial scales in Northern VT. RI%, DI%, and FR% showed more significant influences among different land-use categories. Here, RDI% was used to present the combination of RI% and DI%, which may better represent human-dominated land uses, such residential areas and commercial/industrial areas reflecting regional social and economic development. ΣPFAA levels were more significantly correlated with RDI %, which verifies the potential impact of human activities. In the case of the two PFAA sub-groups, the degree of associations between ΣPFSA and RI, DI, and RDI were much more robust than those of ΣPFCA, suggesting that sources related to human activities may be a more critical influence of PFSA in soils. Fig. 7 displays the geometric mean of ΣPFCA, ΣPFSA, ΣPFAA, and PFOS, the dominant species, within different RDI% ranges (>50 %, 10–50 %, and <10 %) using a spatial scale of 1000 m in Northern and Southern VT as an example. It is worth noting that RDI% strongly associates with the levels of PFOS, ΣPFCA, ΣPFSA, and ΣPFAA-especially in the > 50 % category- which is in good agreement with the correlation results. Typically, higher RDI% would lead to higher levels of PFOS, ΣPFCA, ΣPFSA, and ΣPFAA, verifying that sources related to human activities may be significant contributors to PFAA to soils in Northern VT. Potential causal factors are unclear at the moment due to a lack of data. Theoretically, cleared lands associated with human development may expose soils to higher levels of atmospheric deposition from either local or long-range sources.

Correlations between land-use types and individual PFAA with quantitative detection frequency more significant than 50 % were also evaluated (see Table S16). In Northern VT, the impact of land-use types varied notably for different PFAA. In particular, PFHxA was found to be slightly correlated to DI% and RDI% at different spatial scales, while PFHpA, PFOA, and PFBS had no clear correlation with different land-use types. In contrast, DI% and RDI% had stronger correlations with PFOS, suggesting that human activities may be main sources of PFOS in soils. Meanwhile, other PFAA, including PFNA, PFDA, PFUnDA, and PFOS, were positively related to DI% and RDI%. Such correlations varied depending on the spatial scales, and the highest correlations were observed at spatial scale of 1000 m. RI% was found to pose weaker but positive impacts on these PFNA, PFDA, PFUnDA, and PFOS when spatial scales were increased to more than 500 m. This suggests that human-induced pressure associated with residential land use may be a less critical factor contributing to their presence in soils. FR% was negatively correlated with PFNA, PFDA, and PFUnDA, especially at spatial scales ranging from 500 to 1000 m. The improved correlations between PFNA, PFDA, PFUnDA, PFOS, and related land-use types observed with increased spatial scale suggest that PFAA originating from relevant human activities may be more mobile than other sources.

Different from the trends observed in Northern VT, no notable correlation (Table S17) was observed between land-use types and occurrence of PFAA at all spatial scales in Southern VT except related to ΣPFSA and PFOS were slightly but negatively related to Forest in the range from 250 m to 1000 m. It is worth noting that compared to Northern VT, Southern VT generally has lower population density and only three sites (G5, K6d and K6e) located in Hartford area have RDI% higher than 50 % at all spatial scales. Interestingly, site J6, which

Table 1
Spearman's rank correlation analysis between land-use types (%) and ΣPFCA, ΣPFSA and ΣPFAA in Northern VT.

Buffer = 100 m		RI	DI	RDI	FR	GS	WD	HA	NT
ΣPFCA	r	0.327	0.298	0.401	-0.415	-0.121	-0.263	0.482	-0.482
	p	0.045	0.069	0.013	0.010	0.470	0.111	0.002	0.002
ΣPFSA	r	0.299	0.451	0.505	-0.446	0.122	-0.244	0.403	-0.403
	p	0.069	0.005	0.001	0.005	0.465	0.140	0.012	0.012
ΣPFAA	r	0.334	0.429	0.504	-0.471	0.036	-0.245	0.465	-0.465
	p	0.040	0.007	0.001	0.003	0.831	0.138	0.003	0.003
Buffer = 250 m		**RI**	**DI**	**RDI**	**FR**	**GS**	**WD**	**HA**	**NT**
ΣPFCA	r	0.305	0.325	0.454	-0.386	-0.367	-0.357	0.491	-0.491
	p	0.063	0.047	0.004	0.017	0.023	0.028	0.002	0.002
ΣPFSA	r	0.321	0.558	0.618	-0.472	-0.150	-0.327	0.491	-0.491
	p	0.049	<0.001	<0.001	0.003	0.370	0.045	0.002	0.002
ΣPFAA	r	0.330	0.501	0.597	-0.466	-0.274	-0.362	0.524	-0.524
	p	0.043	0.001	0.000	0.003	0.095	0.025	0.001	0.001
Buffer = 500 m		**RI**	**DI**	**RDI**	**FR**	**GS**	**WD**	**HA**	**NT**
ΣPFCA	r	0.335	0.432	0.443	-0.342	-0.345	-0.256	0.467	-0.467
	p	0.040	0.007	0.005	0.035	0.034	0.121	0.003	0.003
ΣPFSA	r	0.444	0.632	0.651	-0.487	-0.118	-0.304	0.529	-0.529
	p	0.005	<0.001	0.000	<0.001	0.482	0.064	0.001	0.001
ΣPFAA	r	0.423	0.596	0.617	-0.457	-0.230	-0.326	0.541	-0.541
	p	0.008	<0.001	<0.001	0.004	0.165	0.046	0.000	0.000
Buffer = 1000 m		**RI**	**DI**	**RDI**	**FR**	**GS**	**WD**	**HA**	**NT**
ΣPFCA	r	0.415	0.439	0.473	-0.329	-0.239	-0.093	0.437	-0.437
	p	0.010	0.006	0.003	0.044	0.149	0.577	0.006	0.006
ΣPFSA	r	0.635	0.652	0.682	-0.488	-0.034	-0.099	0.535	-0.535
	p	<0.001	<0.001	<0.001	0.002	0.837	0.553	0.001	0.001
ΣPFAA	r	0.589	0.605	0.644	-0.453	-0.133	-0.139	0.522	-0.522
	p	<0.001	<0.001	<0.001	<0.001	0.427	0.404	0.001	0.001

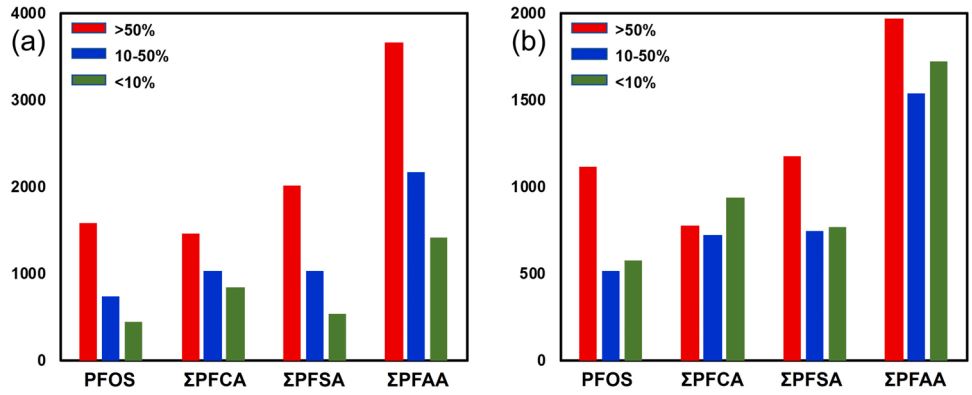

Fig. 7. The geometric means of PFOS, ΣPFCA, ΣPFSA, and ΣPFAA within different RDI% ranges (>50 %, 10–50 %, and <10 %, Buffer = 1000 m) in Northern VT (a) and Southern VT (b).

showed highest ΣPFAA level, its RDI% dropped to 32.2 % when spatial scale increased to 1000 m. Overall, lack of correlation suggests that PFAA released by local sources are less important factor affecting soil PFAA levels.

To assess the spatial variability of PFAA levels in VT surface soils, a geostatistical method called ordinary Kriging method was adopted. As displayed in Fig. 8, clear differences can be observed in the geographical distribution pattern of ΣPFSA (Fig. 8(b)) and ΣPFCA (Fig. 8(c)), but higher levels of ΣPFSA, ΣPFCA as well as ΣPFAA (Fig. 8(a)) were mainly distributed in the northern part of VT, especially around CV+CH area, which is most populous in VT. In the case of individual PFAA (Fig. 8(d–f) and Fig. S3), their "hot-spots" usually located in different areas. PFOS (Fig. 8(d)), PFNA (Fig. 8(f)), PFDA (Fig. S3(c)) and PFUnDA (Fig. S3(d)) showed similar spatial distribution patterns, where their most noticeable "hot-spots" could be identified in the middle of CV area, which has the denser population and is more developed suggesting that these compounds may be more significantly impacted by local human-related activities. Meanwhile, for PFNA and PFDA, second relevant "hot-spots" embodied around northern SVP area (Hartford) with relative higher population density. Although J6 and K6e were regarded as outlier and not used for prediction, their high level of PFAA including PFNA and PFDA also suggest that local PFAA sources may exist. PFHxA (Fig. S3(b)) and PFBS (Fig. S3(e)) shows similar spatial patterns, where higher levels appeared around area with higher population density implying that local human related activities may contribute to their occurrence in soils. In particular, their primary "hot-spots" located in around northern area of NGM and NVP, and also presented higher levels in central CV and northern SVP. No remarkable spatial distribution variation was observed for PFHpA suggesting that PFHpA (Fig. S3(a)) was relatively evenly distributed across VT, while PFOA the most abundant PFCA species tend to be lower in NEH and SVP area. Similar to PFOA, PFHpA were found to be not significantly related to land-use types and population density, local sources may be a minor factor contributing to their occurrence in VT soils. It is important to point out that here the predictions were based on limited number of surface soil samples, and may be validated and further improved with further studies employing higher sampling frequency and higher sampling density.

3.5. Potential source analysis

Source identification was investigated by combining land-use analysis with multivariable statistics. Spearman's rank correlation analysis was utilized to study the correlations among individual PFAA with a quantitative detection frequency higher than 50 %. Particularly, strong and positive correlations generally indicate similar sources, transport processes, and transformation processes among different PFAS (Qi et al., 2016; Young et al., 2007). Moreover, as previously reported by other researchers including Rankin et al (Rankin et al., 2016)., Washington et al (Washington et al., 2020)., and Young et al (Young et al., 2007)., ratios of individual PFAA may be indicators of potential sources, and were also examined in our study (data not shown) to assist potential source searching.

PFOA has been phased out by alternatives with shorter alkyl chains like PFHpA and PFHxA in USA. Nevertheless, PFOA and its precursors are still widely applied in both domestic and industrial uses (Prevedouros et al., 2006), and thus can be released to the environment during manufacturing and use of PFOA/precursors-containing products (Li et al., 2020). Unsurprisingly, PFOA was the dominant PFCA species in VT surface soils, nevertheless, PFOA did not show clear correlation with population density and land use type in VT. However, similar to Rankin et al.'s study, PFOA/PFNA of most samples (>70 %) across VT fell into range from 1:1–6:1, which indicates that atmospheric oxidation of precursors like FTOH may be sources to PFOA in the surface soils (Rankin et al., 2016). Only E5 had a PFOA/PFNA ratio > 8:1, indicating potential direct release and deposition of PFOA. Interestingly, E5 was one of the sites with high ΣPFAA but low population density, and thus more investigation may be needed to identify the potential existence of PFAA sources around the site.

In Northern VT, PFNA, PFDA, and PFUnDA had significant positive correlations with each other (Table 2). Meanwhile, they presented slight to moderate positive correlations with PFHxA and PFOS, implying that they may share some common sources. According to land-use analysis, all these PFAA were positively related to HA% (RI, DI, or RDI), revealing that anthropogenic sources or influences contribute significantly to their occurrence in surface soils. It has been widely reported that PFNA, PFDA, and PFUnDA in the environment may originate from degradation of fluorotelomer precursors like fluorotelomer alcohols (FTOH) and fluorotelomer sulfonates (FTSA) through long-range atmospheric and hydrospheric transport (Lu et al., 2015; Li et al., 2017; Kwok et al., 2015). Further, land-use analysis revealed that those compounds may come from direct releases of fluorinated polymer products (e.g., ski waxes, dessert and bread wrappers, sandwich and burger wrappers, etc.) (Schaider et al., 2017; Grønnestad et al., 2019) due to related local human activities. The trend of PFOS occurrence in Northern VT indicates substantial impacts of direct anthropogenic sources as it was more abundant in areas with higher population densities, and thus PFOS may be mainly derived from local point sources, including industrial emissions such as metal plating, firefighting foams, commercial consumer products such as food packaging, and sludges from wastewater treatment plants. In addition, though the production of PFOS has been phased out in the USA since 2002, deposition from historical discharges, long-range atmospheric transport and deposition, and relevant products/derivatives/precursors imported from other countries can still be important PFOS sources in surface soils (Wang et al., 2018, 2017; Meng et al., 2018).

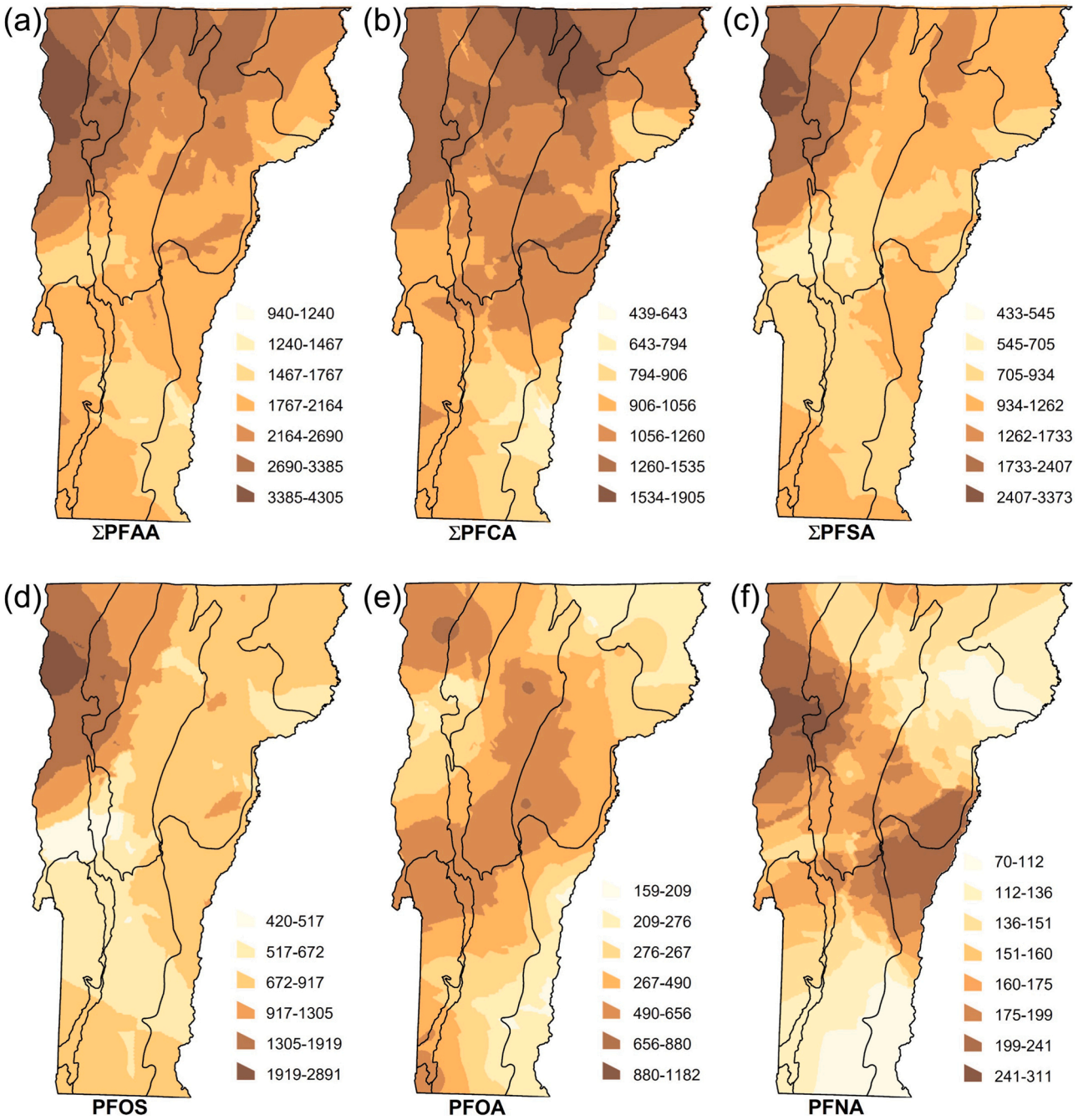

Fig. 8. Spatial distribution levels of ΣPFAA (a), ΣPFCA (b), ΣPFSA (c), PFOS (d), PFOA (e) and PFNA (f) in VT background surface soils predicated by ordinary Kriging interpolation method.

PFHpA showed a slightly positive correlation with PFOA in Northern VT, indicating potential common sources and similar environmental fate. Though PFHxA did not show clear correlation with land-use type, PFHxA was slightly and positively correlated with PFBS and PFNA. Both PFHxA and PFBS tends to exist in areas with higher population density including Burlington, Newport, and Hartford areas, which implies that human activities and local sources may impact their occurrence in surface soil. Particularly, PFHxA and other compounds with shorter alkyl chains are alternatives for C8 products due to the ongoing substitution strategy adopted by industries (Calafat et al., 2019; Li et al., 2020; Wang et al., 2014). Therefore, the occurrence of PFHxA in soils could potentially be attributed to the use of relevant products/precursors and atmospheric degradation of precursors like 6:2FTOH. PFBS was also slightly positively correlated with PFOS, which could be related to the fact that PFBS and its precursors, such as N-methylperfluorobutane sulfonamidoethanol (MeFBSE) are alternative chemicals to PFOS-based products (Lam et al., 2016; D'Eon et al., 2006). Although levels of precursor compounds were not evaluated in this study, it is important to point out that precursor degradation may be another source for PFBS, PFOS as well as other PFAA.

In the case of Southern VT, PFOA was also positively correlated to PFHpA, and PFOS was still found to be closely related to PFNA, PFDA, and PFUnDA (Table S18, SI), but the correlation among PFNA, PFDA, and PFUnDA were weaker compared to those found in the northern area, and no clear correlation was observed between PFNA and PFUnDA. In addition, these compounds did not show significant correlation with HA % (DI%, RI%, and RDI%). Nevertheless, as displayed in Fig. 8 and Fig. S3, relatively higher levels of PFOS, PFOA, PFHpA, PFDA, PFUnDA

Table 2
Spearman's rank correlation analysis among individual PFAA in Northern VT.

		PFHxA	PFHpA	PFOA	PFNA	PFDA	PFUnDA	PFBS	PFOS
PFHxA	r	1	0.301	-0.046	0.545	0.474	0.505	0.682	0.394
	p	N.A	0.066	0.786	<0.001	0.003	0.001	<0.001	0.014
PFHpA	r	0.301	1	0.396	0.294	0.147	-0.010	0.235	0.181
	p	0.066	N.A	0.014	0.073	0.377	0.954	0.155	0.277
PFOA	r	-0.046	0.396	1	0.309	0.107	-0.080	-0.110	0.277
	p	0.786	0.014	N.A	0.059	0.523	0.635	0.512	0.092
PFNA	r	0.545	0.294	0.309	1	0.720	0.522	0.472	0.652
	p	0.000	0.073	0.059	N.A	<0.001	0.001	0.003	<0.001
PFDA	r	0.474	0.147	0.107	0.720	1	0.827	0.464	0.808
	p	0.003	0.377	0.523	<0.001	N.A	<0.001	0.003	<0.001
PFUnDA	r	0.505	-0.010	-0.080	0.522	0.827	1	0.442	0.652
	p	0.001	0.954	0.635	0.001	<0.001	N.A	0.005	<0.001
PFBS	r	0.682	0.235	-0.110	0.472	0.464	0.442	1	0.368
	p	<0.001	0.155	0.512	0.003	0.003	0.005	N.A	0.023
PFOS	r	0.394	0.181	0.277	0.652	0.808	0.652	0.368	1
	p	0.014	0.277	0.092	<0.001	<0.001	<0.001	0.023	N.A

* N.A: Not applicable

may exist in the southwest of VT, especially around Bennington area. Historically, ChemFab factory operated in Northern Bennington from 1978 to 2002 emitted PFOA and other PFAS from smokestacks. Though the factory was closed many years ago, presence of PFOA has been continuously observed in the surround areas. For instance, in 2016, VT Department of Environmental Conservation (VT DEC) reported PFOA contamination in more than 400 drinking water wells with a maximum level of 4600 ppt and some soil samples with a maximum level of 46 ppb in Bennington and North Bennington, respectively. Recently, Schroeder et al. collected water and soil samples (30–40 cm) from sites regarded as forest landscapes on conserved lands with minimal human disturbance but also had specific spatial relations to the air-emission sources around Bennington, VT and Hoosick Falls, NY (New York State) (Schroeder et al., 2021). Particularly, they divided sample sites into five regions based on wind patterns (dominantly west to east), including Bennington local (near industrial sites), Downwind, north of wind pattern, upward and far-field of the emission source, and found much higher PFOA levels in the Bennington local and Downwind (Schroeder et al., 2021). Similarly, PFHpA and PFHxA were more frequently detected in the downwind area, while PFOS, which was claimed not used by local industries, its concentration did not show significant differences among various regions (Schroeder et al., 2021). Interestingly, our predicted distributions of PFOA, PFHpA, PFDA, PFUnDA were less abundant in areas located in the north and east of Bennington areas, which matched their observation. Moreover, the concentrations of PFOA, PFOS detected in their study also fell into the prediction ranges of Bennington and adjacent areas in our study.

It is noteworthy that, VT, the Green Mountain State, is an iconic state for skiers and snowboarders. It has been reported that fluorinated ski waxes may be significant PFAA sources (Carlson and Tupper, 2020; Plassmann and Berger, 2013), and therefore, ski wax and related products and activities may be possible contributors to occurrence of PFAA in VT surface soil. Further studies are necessary to better elaborate the potential impacts of ski related activities on PFAA levels in VT surface soils. Similarly, other potential local sources also need to be systematically examined to illustrate how human activities may impact PFAA in VT surface soils. Thus far, understanding of sources, fate and transport of PFAS in the environment are still limited, and therefore, further research is needed. In this study, only 17 PFAA were studied in VT surface soils, while their precursors and other emerging PFAS were not included. Indeed, more future studies are needed to achieve better understanding towards not only identification of potential sources of PFAS to surface soils, but also their transport and fate, transformation in different environmental compartments as well as potential exposure risk to human health.

Overall, the findings of this study have implications for establishing cleanup criteria for PFAS contaminated sites. For instance, an evaluation of local anthropogenic background levels is appropriate at a cleanup site whenever it is suspected that specific contaminants detected above applicable cleanup criteria may be equal to, or less than, anthropogenic background concentrations. If the contaminant concentration exceeds risk-based criteria, cleanup or other risk management measures are typically required. Cleanup is not needed under current rules if the chemical is present due to natural soil conditions, even if the concentrations exceed risk-based criteria. Consequently, it is vital to manage several sites to determine whether the presence of PFAA represents background conditions.

4. Conclusions

The present study provides insights into anthropogenic background concentrations of PFAA and the influence of total organic carbon and land-use types on the geographic distribution of different types of PFAA in VT surface soils. Overall, the majority of 17 PFAA were detected more or less ubiquitous across VT, with PFOS, PFNA, and PFOA were found to be the three predominant compounds. The concentration of ∑PFAA varied significantly among sampling locations, ranging from 540 to 36,000 ng/kg. Exceedingly high concentrations of PFAA at three different sampling locations (J6, K6e, and E5) were attributed to site-specific unknown historical events related to PFAA contamination. PFCA showed stronger and positive correlations with soil total organic carbon content when compared with PFSA. Land-use analysis revealed differences in the distribution of PFAA among geographical regions. Generally, Northern VT showed relatively higher levels of ∑PFAA than Southern VT. Specifically, ∑PFAA, PFOS, PFHxA, PFNA, PFDA, and PFUnDA were found to be closely related to land-use types in Northern VT, potentially suggesting stronger influences of direct human-induced sources, including domestic and industrial activities in this region. Conversely, the lack of such correlations in Southern VT suggests that concentrated sources related to human activities may be less critical contributors to the occurrence of PFAA in surface soils. In contrast, non-point sources like surface runoff and atmospheric deposition may be more critical. PFAS background levels must be taken into account prior to initiation of any future risk-based PFAS contamination management measures. Background datasets can be used by practitioners and regulatory authorities to contextualize data collected for site characterization and remediation. Requirements and guidance for using background datasets depends upon site-specific and regulatory considerations, with common approaches being calculation of background threshold values and hypothesis testing to compare site and background data distribution. There is still a paucity of data, and our study calls for long-term monitoring of PFAS in soils and data collection for assessment of PFAS

pollution and establishing cleanup standards.

Environmental implication

Evidence to date suggests that a diverse perfluoroalkyl acids (PFAA) are ubiquitous in the environment, persistent, bio-accumulative, and toxic. In some instances, PFAA concentrations in the so-called "hot-spots" may reach levels many times higher than the "background soil concentration." This study defines the typical "background soil concentrations of PFAA" in a rural state like Vermont. In addition, this study provides unique insight into the occurence and distribution of different types of PFAA influenced by soil total organic carbon, geological conditions, and artificial land-use type including human activities vs. nature. These background data will be of much use to state regulators for setting cleanup PFAS surface soils standards and future PFAS risk management.

CRediT authorship contribution statement

Wenyu Zhu: Methodology, Data curation and analysis, Statistical analysis, Visualization, and Writing – original draft, Writing – review & editing. **Kamruzzaman Khan:** TOC and Solids analysis, Methodology. **Elliot Maker:** Sample collection and processing, Geographic information system (GIS) analysis. **Harrison Roakes:** Field sampling, Methodology, Writing. **Stephen Zemba:** Conceptualization, Methodology, Writing – review & editing. **Kristen Underwood:** GIS analysis and interpretation, writing. **Appala Raju Badireddy:** Supervision, Conceptualization, Methodology, Integration and analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2022.129479.

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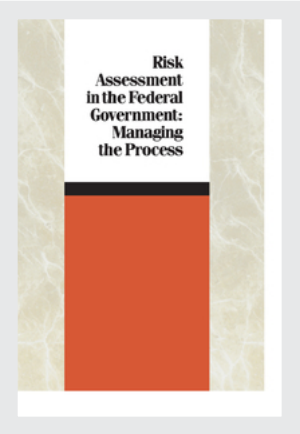

Risk Assessment in the Federal Government: Managing the Process (1983)

DETAILS

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Committee on the Institutional Means for Assessment of Risks to Public Health
Commission on Life Sciences
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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competencies and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The National Research Council was established by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and of advising the federal government. The Council operates in accordance with general policies determined by the Academy under the authority of its congressional charter of 1863, which establishes the Academy as a private, nonprofit, self-governing membership corporation. The Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in the conduct of their services to the government, the public, and the scientific and engineering communities. It is administered jointly by both Academies and the Institute of Medicine. The National Academy of Engineering and the Institute of Medicine were established in 1964 and 1970, respectively, under the charter of the National Academy of Sciences.

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NATIONAL RESEARCH COUNCIL
2101 CONSTITUTION AVENUE WASHINGTON, D. C. 20418
OFFICE OF THE CHAIRMAN

March 1, 1983

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane Rockville, MD 20857

Dear Dr. Hayes:

I am pleased to transmit the enclosed report entitled "Risk Assessment in the Federal Government: Managing the Process." This study was authorized by P.L. 96–528 and carried out by a committee of the National Research Council's Commission on Life Sciences with support from the Food and Drug Administration under Contract No. 223–81–8251.

The Congress made provision for this study to strengthen the reliability and objectivity of scientific assessment that forms the basis for federal regulatory policies applicable to carcinogens and other public health hazards. Federal agencies that perform risk assessments are often hard pressed to clearly and convincingly present the scientific basis for their regulatory decision. In the recent past, for example, decisions on saccharin, nitrites in food, formaldehyde use in home insulations, asbestos, air pollutants and a host of other substances have been called into question.

The report recommends no radical changes in the organizational arrangements for performing risk assessments. Rather, the committee finds that the basic problem in risk assessment is the incompleteness of data, a problem not remedied by changing the organizational arrangement for performance of the assessments. Instead, the committee has suggested a course of action to improve the process within the practical constraints that exist.

THE NATIONAL RESEARCH COUNCIL IS THE PRINCIPAL OPERATING AGENCY OF THE NATIONAL ACADEMY OF SCIENCES AND THE NATIONAL ACADEMY OF ENGINEERING TO SERVE GOVERNMENT AND OTHER ORGANIZATIONS.

Arthur Hull Hayes, Jr., M.D.
March 1, 1993
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One proposal by the committee requires explanation. It would provide that there be established under Academy auspices a Board on Risk Assessment Methods. This recommendation emerges strictly from the committee's internal deliberation. The committee alone is responsible for the substantive contents and findings of the report. Were a request made to the Academy along the lines of that particular recommendation to establish such a Board, the request would be considered de novo by the appropriate governing bodies of the institution.

Yours sincerely,

Frank Press
Chairman

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REP. WILLIAM C. WAMPLER (D-VA), U.S. House of Representatives

Preface

In response to a directive from the Congress of the United States, the Food and Drug Administration contracted with the National Academy of Sciences to conduct a study of the institutional means for risk assessment. The Committee on the Institutional Means for Assessment of Risks to Public Health was formed in the National Research Council's Commission on Life Sciences in October 1981 and completed its work in January 1983. The members of the Committee were chosen to represent a broad array of backgrounds and special skills, both in the technology of risk assessment and in the formulation and application of policy in this field, and brought together extensive experience in industry, government, and academic life.

The Committee, with outstanding staff support, reviewed much of the published literature on risk assessment, studied the structures and operations of federal regulatory and research agencies, analyzed the history of regulation of selected chemicals, and sought and received the judgments of some exceptionally knowledgeable people. We are most grateful for the assistance so generously provided to us, but, of course, the responsibility for this report is entirely ours.

The Committee has sought to examine and codify past experience with risk assessment and relate that experience to patterns and practices. Our judgments are necessarily subjective, but we have endeavored to be impartial. In the process, we developed a disinclination for sweeping changes; we believe that more gradual, evolutionary alterations will result in greater improvements in the conduct and use of risk assessment.

REUEL A. STALLONES
Chairman

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Risk Assessment in the Federal Government: Managing the Process

Summary

SETTING

This report explores the intricate relations between science and policy in a field that is the subject of much debate—the assessment of the risk of cancer and other adverse health effects associated with exposure of humans to toxic substances. It is a report of a search for the institutional mechanisms that best foster a constructive partnership between science and government, mechanisms to ensure that government regulation rests on the best available scientific knowledge and to preserve the integrity of scientific data and judgments in the unavoidable collision of the contending interests that accompany most important regulatory decisions.

Many decisions of federal agencies in regulating chronic health hazards have been bitterly controversial. The roots of the controversy lie in improvements in scientific and technologic capability to detect potentially hazardous chemicals, in changes in public expectations and concerns about health protection, and in the fact that the costs and benefits of regulatory policies fall unequally on different groups within American society.

The decade of the 1970s was a period of heightened public concern about the effects of technology on the environment. Individuals and groups urged strict government regulation as scientific evidence emerged that various chemical substances may induce cancers or other chronic health effects in humans, and new government programs were established to control potential hazards. The evidence of health effects of a few chemicals, such as asbestos, has been clear; in many more cases the evidence is meager and indirect. To aid decision-making,

agencies have developed procedures for identifying chronic health hazards and estimating the risks to human health posed by products and activities. However, rather than alleviating the controversy attending regulatory decisions, the procedures themselves have become a focus of criticism by scientists, industry representatives, and public-interest groups.

STUDY OBJECTIVES AND SCOPE

The Committee on Institutional Means for Assessment of Risks to Public Health was formed, in response to a congressional directive, to fulfill three primary objectives:

- To assess the merits of separating the analytic functions of developing risk assessments from the regulatory functions of making policy decisions.
- To consider the feasibility of designating a single organization to do risk assessments for all regulatory agencies.
- To consider the feasibility of developing uniform risk assessment guidelines for use by all regulatory agencies.

The Committee considered the current practice of risk assessment and its relation to the process of regulation of hazards to human health, past efforts to develop and use risk assessment guidelines, the experience of government regulatory agencies with different administrative arrangements for risk assessment, and various proposals to modify risk assessment procedures. Our study was directed primarily, although not exclusively, to the issue of increased risk of cancer resulting from exposure to chemicals in the environment, an issue that has aroused great public concern in recent years, as illustrated by the controversies involving the control of saccharin, asbestos, and formaldehyde. Despite this emphasis, however, our conclusions and recommendations are applicable in some degree across the broad field of environmental health.

Criticisms of risk assessment have ranged broadly from details of the process to administrative management to statutory authority. The mandate to this Committee did not include examination of the scientific issues involved in risk assessment or the broad social policy questions

that have been raised. The Committee's more limited purpose was to examine whether altered institutional arrangements or procedures can improve regulatory performance.

THE NATURE OF RISK ASSESSMENT

Regulatory actions are based on two distinct elements, risk assessment , the subject of this study, and risk management. Risk assessment is the use of the factual base to define the health effects of exposure of individuals or populations to hazardous materials and situations. Risk management is the process of weighing policy alternatives and selecting the most appropriate regulatory action, integrating the results of risk assessment with engineering data and with social, economic, and political concerns to reach a decision.

Risk assessments contain some or all of the following four steps:

- Hazard identification: The determination of whether a particular chemical is or is not causally linked to particular health effects.
- Dose-response assessment: The determination of the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.
- Exposure assessment: The determination of the extent of human exposure before or after application of regulatory controls.
- Risk characterization: The description of the nature and often the magnitude of human risk, including attendant uncertainty.

In each step, a number of decision points (components) occur where risk to human health can only be inferred from the available evidence. Both scientific judgments and policy choices may be involved in selecting from among possible inferential bridges, and we have used the term risk assessment policy to differentiate those judgments and choices from the broader social and economic policy issues that are inherent in risk management decisions. At least some of the controversy surrounding regulatory actions has resulted from a blurring of the distinction between risk assessment policy and risk management policy.

UNIFORM GUIDELINES FOR RISK ASSESSMENT

An inference guideline is an explicit statement of a predetermined choice among alternative methods (inference options) that might be used to infer human risk from data that are not fully adequate or are not drawn directly from human experience. For example, a guideline might specify the mathematical model to be used to estimate the effects of exposure at low doses on the basis of the effects of exposure at high doses.

Over the last 2 decades, most federal regulatory agencies and other institutions responsible for risk assessment of toxic chemicals have sought to develop such guidelines. Their efforts have met with varied success. Agencies have cited several reasons for writing guidelines: to provide a systematic way to meet statutory requirements, to inform the public and regulated industries of agency policies, to stimulate public comment on those policies, to avoid arguing generic questions anew in each specific case, and to foster consistency and continuity of approach. Interagency guidelines for carcinogens, although short-lived, were developed by the agencies of the Interagency Regulatory Liaison Group (IRLG) and adopted by the President's Regulatory Council in 1979. The stated objective of that effort was to reduce inconsistency, duplication of effort, and lack of coordination among the federal agencies.

The form of guidelines varies widely. Some guidelines are comprehensive and detailed, addressing most of the components of risk assessment and describing underlying scientific concepts; others address only a few broad principles. Guidelines differ greatly in their degree of flexibility, i.e., the degree to which they permit assessors to consider scientific evidence that may justify departures from the prescribed inference options. And they vary in the legal authority vested in them: some are adopted as formal regulations and others by less formal means.

The Committee concludes that guidelines are feasible and, if properly designed, desirable; that clear statements of the inferences to be made in each step would be of advantage to the regulatory agencies, to the industries concerned, and to the general public; and that guidelines should be used uniformly by the governmental agencies.

INSTITUTIONAL ARRANGEMENTS FOR RISK ASSESSMENT

Dissatisfaction with government regulatory actions has led to proposals to restructure the institutional arrangements for risk assessment by:

- Organizational separation of risk assessment from risk management.
- Centralization of risk assessment activities in a single organization to serve all the regulatory agencies.

Four federal agencies—the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), Occupational Safety and Health Administration (OSHA), and Consumer Product Safety Commission (CPSC)—have been given primary authority to regulate activities and substances that pose chronic health risks, and these four agencies' past actions have inspired many of the proposals for institutional change. The Committee reviewed a number of agency structures and procedures in an attempt to determine the merits of institutional separation and centralization. Examples were selected to illustrate different degrees of separation and centralization in the four agencies. Independent scientific review panels have been used to obtain some of the advantages proposed for organizational separation, and some of their experiences were examined.

Cross-agency comparisons are difficult, because the regulatory agencies and their various programs differ markedly in structure, procedures, personnel characteristics, administrative history, and statutory direction. In addition, agencies and programs change, and practices adhered to for several years may be altered substantially. These practical limitations to the evaluation of agency structures and practices led the Committee to conclude that predicting the likely effects of organizational rearrangements on agency performance of risk assessment is unavoidably judgmental. However, the available evidence shows no clear advantage of one administrative structure over another.

CONCLUSIONS AND MAJOR RECOMMENDATIONS

Dissatisfaction with the actions of federal regulatory agencies is often expressed as criticism of the conduct and administration of the risk assessment process. The

Committee believes that the basic problem in risk assessment is the sparseness and uncertainty of the scientific knowledge of the health hazards addressed, and this problem has no ready solution. The field has been developing rapidly, and the greatest improvements in risk assessment result from the acquisition of more and better data, which decreases the need to rely on inference and informed judgment to bridge gaps in knowledge.

Proposals to separate the administrative responsibility for risk assessment from risk management imply that the change would lead to improved risk assessment and hence better risk management decisions. Administrative relocation will not, however, improve the knowledge base, and, because risk assessment is only one element in the formulation of regulatory actions, even considerable improvements in risk assessment cannot be expected to eliminate controversy over those actions.

Organizational separation may have the advantage of establishing firmly the distinction between risk assessment and risk management, but it also has some disadvantages. The importance of distinguishing between risk assessment and risk management does not imply that they should be isolated from each other; in practice they interact, and communication in both directions is desirable and should not be disrupted. Institutional separation would surely reduce the responsiveness of the risk assessment process to the needs of the regulatory agencies for timely reports in accord with their priorities. In addition to the operational disadvantages, the disruption of current patterns of activity would be great, and the benefits uncertain. On balance, the Committee believes that transfer of risk assessment functions to an organization separate from the regulatory agencies is not appropriate.

We believe that risk assessment can be improved more surely and more effectively by adopting a program with three major parts: (A) implementation of procedural changes to ensure that individual assessments routinely take full advantage of the available scientific knowledge, while preserving the diversified approaches to the administration of risk assessment necessary to accommodate the varied needs of federal regulatory programs; (B) standardization of analytic procedures among federal programs through the development and use of uniform inference guidelines; and (C) creation of a mechanism that will ensure orderly and continuing review and modification of

risk assessment procedures as the scientific knowledge base expands.

(A) We recommend that regulatory agencies take steps to establish and maintain a clear conceptual distinction between assessment of risks and consideration of risk management alternatives; that is, the scientific findings and policy judgments embodied in risk assessments should be explicitly distinguished from the political, economic, and technical considerations that influence the design and choice of regulatory strategies.

We agree with proponents of such measures as the American Industrial Health Council's proposed science panel and H.R. 638 that efforts should be made by regulators and others to distinguish clearly between the assessment of risk and the choice of regulatory options.

We advocate the adoption of specific procedural measures that can be introduced under current arrangements. These measures include timely independent scientific review of major agency risk assessments and, to facilitate both scientific and public review of risk assessments, the routine preparation of written risk assessments that explicitly state the basis of choice among inference options.

(B) We recommend that uniform inference guidelines be developed for the use of federal regulatory agencies in the risk assessment process.

The Committee endorses the development and use of guidelines for risk assessment. These guidelines, which would structure the interpretation of scientific and technical information relevant to the assessment of health risks, should be followed by all federal agencies. They should address all elements of risk assessment, but allow flexibility to consider unique scientific evidence in particular instances.

The use of uniform guidelines would promote clarity, completeness, and consistency in risk assessment; would clarify the relative roles of scientific and other factors in risk assessment policy; would help to ensure that assessments reflect the latest scientific understanding; and would enable regulated parties to anticipate government decisions. In addition, adherence to inference

guidelines will aid in maintaining the distinction between risk assessment and risk management.

(C) We recommend to the Congress that a Board on Risk Assessment Methods be established to perform the following functions:

(1) To assess critically the evolving scientific basis of risk assessment and to make explicit the underlying assumptions and policy ramifications of the inference options in each component of the risk assessment process.
(2) To draft and periodically to revise recommended inference guidelines for risk assessment for adoption and use by federal regulatory agencies.
(3) To study agency experience with risk assessment and evaluate the usefulness of the guidelines.
(4) To identify research needs in the risk assessment field and in relevant underlying disciplines.

The Committee concludes that success in improving the risk assessment process requires the establishment of an independent board of scientific stature. Such a board can serve as a continuing locus of discussion about ways to improve scientific and procedural aspects of risk assessment.

Introduction

Through Congress the American public has granted authority to federal administrative agencies to restrict private actions, such as the production and use of chemicals, when this is deemed necessary to protect the health of the public. The 1970s are notable for the large number of new federal regulatory laws that are applicable to the environment, both in the workplace and in the community. These laws reflect a dramatic and relatively rapid shift in public priorities toward the protection of health. Concurrently with shifts in social priorities, advances in science have contributed to policy problems, for the advances have revealed the extent of the environmental health problem. Some earlier regulatory programs had addressed exposure to toxic chemicals, but they were directed mainly at the risk of poisoning and other acute effects. Much policy-making related to such effects involved routine, short-term, acute animal studies to establish "no-observed-effect" doses and then the straightforward calculation of allowable human exposure based on the application of safety factors to relatively uncomplicated scientific findings. Such an approach reflected little recognition of problems that might be associated with smaller exposures. Cancer, birth defects, and other conditions were seldom seen as preventable by government intervention. Only in the last 15 years has the potential extent of the linkage between such conditions and toxic substances been revealed. The often-cited estimate that a large fraction of all cancers may be attributed to human exposure to toxic agents (including smoking, diet, lifestyle, and occupation) originated fairly recently (Boyland, 1969; Higginson, 1969), and it

was not until the 1970s that regulatory agencies focused their attention on cancer and other chronic health risks.

Scientific advances entered the picture in a second way. The technology that has made it possible to detect relations between particular agents and cancer or other chronic effects has evolved rapidly from the days when exposure through skin-painting and subcutaneous injection were relied on in animal tests of carcinogenicity. Increasingly, epidemiologic investigations have either confirmed the findings of animal experiments or provided evidence that linked exposures to particular chemicals to particular chronic health effects. The introduction of reliable testing methods resulted in broader government testing requirements and, steadily, the discovery of more and more suspect chemicals—many of them in common use—that demanded agency attention. The techniques are still developing, and we are still looking for better ways to design and interpret animal bioassay experiments.

The increase in newly suspect chemicals was accompanied by the development of instruments and procedures that permitted the detection of chemicals at lower and lower concentrations. Even if the number of suspect chemicals had not increased dramatically, these sensitive detection methods would have revealed the presence of such chemicals in concentrations that earlier methods would have missed. Combined with all those changes were the development and refinement of analytic methods of estimating the degree of human risk on the basis of data from human studies and animal experiments.

Public policies are not immediately adaptable to rapid changes in social priorities and scientific advances. Many of the fundamental difficulties of regulatory risk assessment result from attempts to bend old laws and policies to fit newly perceived risks. For instance:

- A regulatory framework based on the traditional approach involving no-observed-effect doses and safety factors is now being applied to health effects for which a no-effect dose cannot be demonstrated, except at zero exposure.
- Regulatory laws and programs designed for the elimination of what was understood to be the very rare event of chronic hazard now operate in the presence of the recognition that many agents are suspect.
- Agencies must evaluate hundreds of chemicals on which no data related to human risk are available and on

which few animal tests were required and many other chemicals that were tested with methods that do not meet modern standards.

- Laws were written and programs designed before current quantitative methods for estimating human risks on the basis of data from animal studies were developed.

DIFFICULTIES IN DECISION-MAKING

Agency decisions regarding potential carcinogens and similar hazards are commonly beset by two types of difficulties: inherent limitations on the power of analysis and practical constraints imposed by external pressures. Several such factors are particularly relevant to the consideration of scientific aspects of risk assessment.

Inherent Limitations

Uncertainty

The dominant analytic difficulty is pervasive uncertainty. Risk assessment draws extensively on science, and a strong scientific basis has developed for linking exposure to chemicals to chronic health effects. However, data may be incomplete, and there is often great uncertainty in estimates of the types, probability, and magnitude of health effects associated with a chemical agent, of the economic effects of a proposed regulatory action, and of the extent of current and possible future human exposures. These problems have no immediate solutions, given the many gaps in our understanding of the causal mechanisms of carcinogenesis and other health effects and in our ability to ascertain the nature or extent of the effects associated with specific exposures. Because our knowledge is limited, conclusive direct evidence of a threat to human health is rare. Fewer than 30 agents are definitely linked with cancer in humans (Tomatis et al., 1978); in contrast, some 1,500 substances are reportedly carcinogenic in animal tests, although they include substances tested in studies of questionable experimental design. We know even less about most chemicals; only about 7,000 of the over 5,000,000 known substances have ever been tested for carcinogenicity (Maugh, 1978) --a small fraction of those theoretically under regulatory jurisdiction. We

know still less about chronic health effects other than cancer.

Ethical considerations prevent deliberate human experimentation with potentially dangerous chemicals, and the length of the latent period for cancer and some other effects greatly complicates epidemiologic studies of uncontrolled human exposures. Animal models must be used to investigate whether exposure to a chemical is related to the incidence of health effects, and the results must be extrapolated to humans. To make judgments amid such uncertainty, risk assessors must rely on a series of assumptions.

Limited Analytic Resources

The number of chemicals in the jurisdiction of federal regulatory agencies is enormous. For example, of the roughly 5,000,000 known chemicals, more than 70,000 are in commercial use (Fishbein, 1980). The Environmental Protection Agency's Chemical Activities Status Report lists about 3,500 chemicals as being under some sort of active consideration in the Agency's various regulatory programs. Similarly, the Food and Drug Administration's food program must cope with over 2,000 food-related chemicals (900 flavors, 700 items listed as "generally recognized as safe," 350 food additives, 175 animal drugs, and 60 color additives) and an additional 12,000 indirect additives (Flamm, 1981).

The many problem chemicals in an agency's jurisdiction compete for attention of analysts and decision-makers. If an agency is considering new action on many substances at once, its scientific staff is stretched thin. Most agencies do not have the analytic resources to do a thorough risk assessment for priority-setting and must rely on less formal methods to ensure that the highest-risk chemicals are examined first.

Complexity

For most chemical agents that might be subject to regulation, a great variety of factors must be assessed, including potential toxicity, extent of human exposure, effectiveness of technologies to reduce exposure, the nature of possible substitute chemicals, effects on and interests of various population groups, and economic effects of

regulatory alternatives. Decision-makers in a regulatory agency may encounter a large amount of highly technical information as they work toward their decisions; many scientific disciplines and technical fields are usually involved. An agency would like to have simple rules and analytic procedures to ensure consistency and competence in its decision-making, but, in the face of scientific uncertainty, such simplicity is difficult to achieve without an inadvertent loss of crucial scientific insight from the decision process.

External Pressures

Public Concern with Health Protection

When the risk involves a serious disease, such as cancer, or birth defects, feelings are likely to run high, particularly if the groups exposed to a chemical are mobilized to express themselves in an agency's deliberations. Such groups insist that regulatory action need not await conclusive evidence of cause and effect and need not be based exclusively on the most scientifically advanced testing methods.

Visible Economic Interests

Although it is rarely known which individuals are likely to be saved from adverse health effects through a regulation that reduces exposure to a particular chemical, those who bear the economic costs of such restrictions can identify themselves without any difficulty. These parties can provide relatively concrete projections of a prospective regulation's inflationary influence, effect on employment, and other immediate economic effects, and such consequences may be substantial. They may question the wisdom of balancing concrete evidence of economic damage against evidence of health protection that depends on a complex series of assumptions derived from sparse and indirect data.

Congressional Action

In fulfilling its role as the legislative voice of popular concerns, Congress can act in ways that influence decision

processes. It can dictate the factors to be included in and excluded from decision-making (the Delaney clause is an example), and it can pass special legislation to preempt agency discretion, as it did in acting to prevent the removal of saccharin from the market.

PROPOSED REFORMS

Under these conditions, it would perhaps be surprising if calls for major reform were not heard. Some have sought to improve the techniques that the government uses to analyze and evaluate risks; for example, the House of Representatives in 1982 passed H.R. 6159 (commonly known as the "Ritter bill"), to establish a government-wide program of research and demonstration projects on quantitative and comparative risk analysis.

Much of the recent controversy is general; it reflects the conflict in values between different groups in society, particularly with regard to the relative importance of economic factors and health protection in the formulation of regulatory decisions. Different groups will inevitably disagree about the degree of risk (if any) that is defined as acceptable in a particular case. However, some criticisms directly address the risk assessment component of the overall decision-making process. Some critics question whether current practices adequately safeguard the quality of the scientific interpretations needed for risk assessment. With a scientific base that is still evolving, with large uncertainties to be addressed in each decision, and with the presence of great external pressures, some see a danger that the scientific interpretations in risk assessments will be distorted by policy considerations, and they seek new institutional safeguards against such distortion.

Among the institutional reforms suggested, two major categories are the focus of this report: reorganization to ensure that risk assessments are protected from inappropriate policy influences and development and use of uniform guidelines for carrying out risk assessments.

Some argue that scientific quality, consistency, and distinction between scientific judgment and policy judgment can be improved through the use of explicit guidelines for agency risk assessments. Such guidelines would specify methods for interpreting scientific data and would seek to limit analysts who confront data gaps or

extrapolation questions to methods that are consistent with the best current scientific judgment. Analysts following the guidelines would find it easier to describe systematically and explicitly the methods that are incorporated in their risk assessments.

Several other recent proposals call for major restructuring of federal processes to separate the risk assessment function organizationally from decision-making. The objectives would be to permit analysts to work independently of policy pressures and to foster consistency of risk assessments. Various approaches have been suggested, including creation of a single body outside the government for the performance or review of risk assessments, creation of a single government unit to conduct risk assessments for the entire government, and creation of separate risk assessment units in particular programs or agencies and systematic review of assessments by independent scientific advisory groups.

THE STUDY

This report responds to a congressional request to examine the merits of the two major types of reform proposal. It is the final report of the National Research Council's Committee on the Institutional Means for Assessment of Risks to Public Health. Chapter I describes the structure of risk assessment, the role of science in the assessment process, and current federal uses of risk assessment. Chapter II examines the feasibility and desirability of the development and use of uniform guidelines. Chapter III reviews various organizational arrangements for risk assessment. The Committee's overall conclusions and recommendations appear in Chapter IV.

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I

The Nature of Risk Assessment

Recent criticisms of the conduct and use of risk assessment by regulatory agencies have led to a wide range of proposed remedies, including changes in regulatory statutes and the development of new methods for assessing risk. The mandate to this Committee was more limited. Our objective was to examine whether alterations in institutional arrangements or procedures, particularly the organizational separation of risk assessment from regulatory decision-making and the use of uniform guidelines for inferring risk from available scientific information, can improve federal risk assessment activities.

Before undertaking to determine whether organizational and procedural reforms could improve the performance and use of risk assessment in the federal government, the Committee examined the state of risk assessment and the regulatory environment in which it is performed. In this chapter, we define risk assessment and differentiate it from other elements in the regulatory process, analyze the types of judgments made in risk assessment, and examine its current government context. Because one chronic health hazard, cancer, was highlighted in the Committee's congressional mandate and has dominated public concern about public health risks in recent years, most of our report focuses on it. Furthermore, because activities in four agencies—the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the Occupational Safety and Health Administration (OSHA), and the Consumer Product Safety Commission (CPSC)—have given rise to many of the proposals for changes in risk assessment practices, our review focuses on these four agencies. The conclusions of this report, although directed primarily at risk assessment of potential carcinogens as performed by these

four agencies, may be applicable to other federal programs to reduce health risks.

TERMINOLOGY

Despite the fact that risk assessment has become a subject that has been extensively discussed in recent years, no standard definitions have evolved, and the same concepts are encountered under different names. The Committee adopted the following terminology for use in this report.

Risk Assessment and Risk Management

We use risk assessment to mean the characterization of the potential adverse health effects of human exposures to environmental hazards. Risk assessments include several elements: description of the potential adverse health effects based on an evaluation of results of epidemiologic, clinical, toxicologic, and environmental research; extrapolation from those results to predict the type and estimate the extent of health effects in humans under given conditions of exposure; judgments as to the number and characteristics of persons exposed at various intensities and durations; and summary judgments on the existence and overall magnitude of the public-health problem. Risk assessment also includes characterization of the uncertainties inherent in the process of inferring risk.

The term risk assessment is often given narrower and broader meanings than we have adopted here. For some observers, the term is synonymous with quantitative risk assessment and emphasizes reliance on numerical results. Our broader definition includes quantification, but also includes qualitative expressions of risk. Quantitative estimates of risk are not always feasible, and they may be eschewed by agencies for policy reasons. Broader uses of the term than ours also embrace analysis of perceived risks, comparisons of risks associated with different regulatory strategies, and occasionally analysis of the economic and social implications of regulatory decisions—functions that we assign to risk management.

The Committee uses the term risk management to describe the process of evaluating alternative regulatory actions and selecting among them. Risk management, which is carried out by regulatory agencies under various legislative

mandates, is an agency decision-making process that entails consideration of political, social, economic, and engineering information with risk-related information to develop, analyze, and compare regulatory options and to select the appropriate regulatory response to a potential chronic health hazard. The selection process necessarily requires the use of value judgments on such issues as the acceptability of risk and the reasonableness of the costs of control.

Steps in Risk Assessment

Risk assessment can be divided into four major steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. A risk assessment might stop with the first step, hazard identification, if no adverse effect is found or if an agency elects to take regulatory action without further analysis, for reasons of policy or statutory mandate.

Of the four steps, hazard identification is the most easily recognized in the actions of regulatory agencies. It is defined here as the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition (cancer, birth defect, etc.). It involves characterizing the nature and strength of the evidence of causation. Although the question of whether a substance causes cancer or other adverse health effects is theoretically a yes-no question, there are few chemicals on which the human data are definitive. Therefore, the question is often restated in terms of effects in laboratory animals or other test systems, e.g., "Does the agent induce cancer in test animals?" Positive answers to such questions are typically taken as evidence that an agent may pose a cancer risk for any exposed humans. Information from short-term in vitro tests and on structural similarity to known chemical hazards may also be considered.

Dose-response assessment is the process of characterizing the relation between the dose of an agent administered or received and the incidence of an adverse health effect in exposed populations and estimating the incidence of the effect as a function of human exposure to the agent. It takes account of intensity of exposure, age pattern of exposure, and possibly other variables that might affect response, such as sex, lifestyle, and other modifying factors. A dose-response assessment usually

requires extrapolation from high to low dose and extrapolation from animals to humans. A dose-response assessment should describe and justify the methods of extrapolation used to predict incidence and should characterize the statistical and biologic uncertainties in these methods.

Exposure assessment is the process of measuring or estimating the intensity, frequency, and duration of human exposures to an agent currently present in the environment or of estimating hypothetical exposures that might arise from the release of new chemicals into the environment. In its most complete form, it describes the magnitude, duration, schedule, and route of exposure; the size, nature, and classes of the human populations exposed; and the uncertainties in all estimates. Exposure assessment is often used to identify feasible prospective control options and to predict the effects of available control technologies on exposure.

Risk characterization is the process of estimating the incidence of a health effect under the various conditions of human exposure described in exposure assessment. It is performed by combining the exposure and dose-response assessments. The summary effects of the uncertainties in the preceding steps are described in this step.

The relations among the four steps of risk assessment and between risk assessment and risk management are depicted in Figure I-1. The type of research information needed for each step is also illustrated.

Scientific Basis for Risk Assessment

Step 1. Hazard Identification

Although risk assessment as it is currently practiced by federal agencies for the estimation of carcinogenic risk contains several relatively new features, the scientific basis for much of the analysis done in risk assessment is well established. This is especially true of the first step in the assessment process, hazard identification. Four general classes of information may be used in this step: epidemiologic data, animal-bioassay data, data on in vitro effects, and comparisons of molecular structure.

Epidemiologic Data

Well-conducted epidemiologic studies that show a positive association between an agent and a disease are

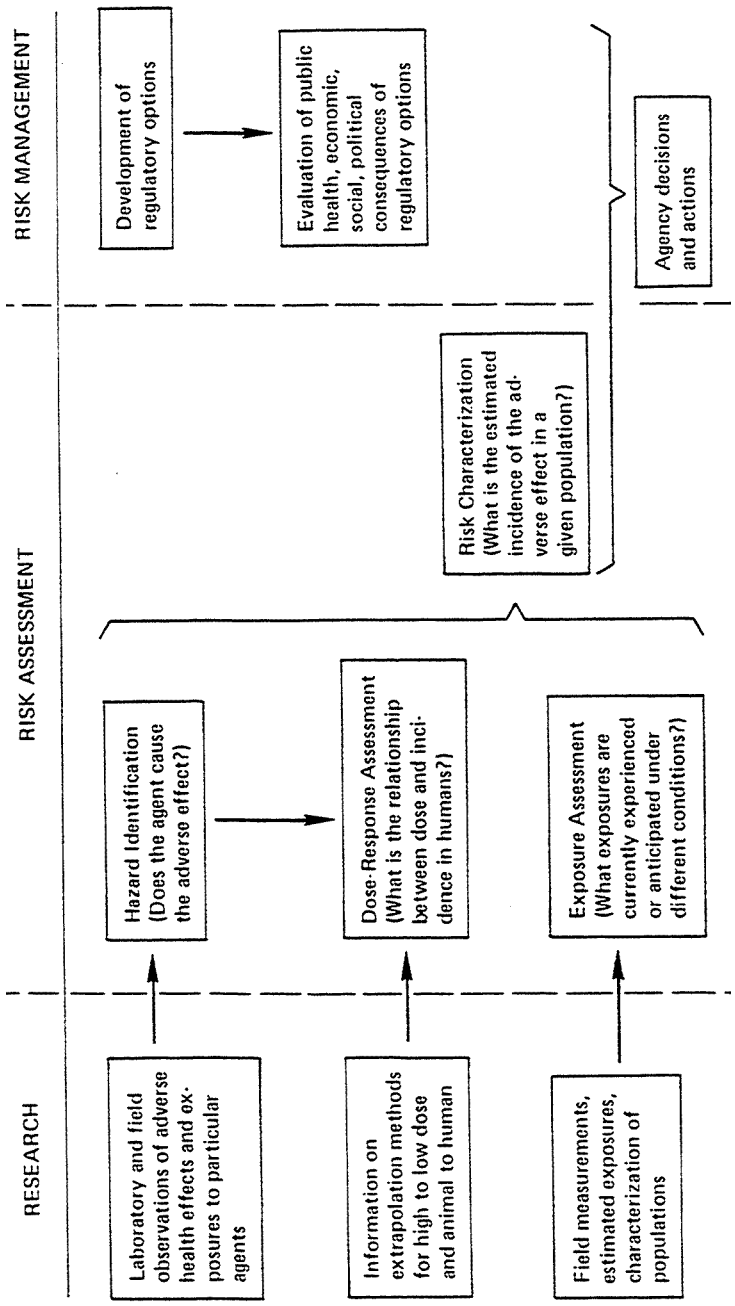

FIGURE I-1 Elements of risk assessment and risk management.

accepted as the most convincing evidence about human risk. This evidence is, however, difficult to accumulate; often the risk is low, the number of persons exposed is small, the latent period between exposure and disease is long, and exposures are mixed and multiple. Thus, epidemiologic data require careful interpretation. Even if these problems are solved satisfactorily, the preponderance of chemicals in the environment has not been studied with epidemiologic methods, and we would not wish to release newly produced substances only to discover years later that they were powerful carcinogenic agents. These limitations require reliance on less direct evidence that a health hazard exists.

Animal-Bioassay Data

The most commonly available data in hazard identification are those obtained from animal bioassays. The inference that results from animal experiments are applicable to humans is fundamental to toxicologic research; this premise underlies much of experimental biology and medicine and is logically extended to the experimental observation of carcinogenic effects. Despite the apparent validity of such inferences and their acceptability by most cancer researchers, there are no doubt occasions in which observations in animals may be of highly uncertain relevance to humans.

Consistently positive results in the two sexes and in several strains and species and higher incidences at higher doses constitute the best evidence of carcinogenicity. More often than not, however, such data are not available. Instead, because of the nature of the effect and the limits of detection of animal tests as they are usually conducted, experimental data leading to a positive finding sometimes barely exceed a statistical threshold and may involve tumor types of uncertain relation to human carcinogenesis. Interpretation of some animal data may therefore be difficult. Notwithstanding uncertainties associated with interpretation of some animal tests, they have, in general, proved to be reliable indicators of carcinogenic properties and will continue to play a pivotal role in efforts to identify carcinogens.

Short-Term Studies

Considerable experimental evidence supports the proposition that most chemical carcinogens are mutagens and that many mutagens are carcinogens. As a result, a positive response in a mutagenicity assay is supportive

evidence that the agent tested is likely to be carcinogenic. Such data, in the absence of a positive animal bioassay, are rarely, if even, sufficient to support a conclusion that an agent is carcinogenic. Because short-term tests are rapid and inexpensive, they are valuable for screening chemicals for potential carcinogenicity and lending additional support to observations from animal and epidemiologic investigations.

Comparisons of Molecular Structure

Comparison of an agent's chemical or physical properties with those of known carcinogens provides some evidence of potential carcinogenicity. Experimental data support such associations for a few structural classes; however, such studies are best used to identify potential carcinogens for further investigation and may be useful in priority-setting for carcinogenicity testing.

Step 2. Dose-Response Assessment

In a small number of instances, epidemiologic data permit a dose-response relation to be developed directly from observations of exposure and health effects in humans. If epidemiologic data are available, extrapolations from the exposures observed in the study to lower exposures experienced by the general population are often necessary. Such extrapolations introduce uncertainty into the estimates of risk for the general population. Uncertainties also arise because the general population includes some people, such as children, who may be more susceptible than people in the sample from which the epidemiologic data were developed.

The absence of useful human data is common for most chemicals being assessed for carcinogenic effect, and dose-response assessment usually entails evaluating tests that were performed on rats or mice. The tests, however, typically have been designed for hazard identification, rather than for determining dose-response relations. Under current testing practice, one group of animals is given the highest dose that can be tolerated, a second group is exposed at half that dose, and a control group is not exposed. (The use of high doses is necessary to maximize the sensitivity of the study for determining whether the agent being tested has carcinogenic potential.) A finding in such studies that increased exposure leads to an increased incidence has been used primarily

to corroborate hazard identification, that is, to show that the agent does indeed induce the adverse health effect.

The testing of chemicals at high doses has been challenged by some scientists who argue that metabolism of chemicals differs at high and low doses; i.e., high doses may overwhelm normal detoxification mechanisms and provide results that would not occur at the lower doses to which humans are exposed. An additional factor that is often raised to challenge the validity of animal data to indicate effects in man is that metabolic differences among animal species should be considered when animal test results are analyzed. Metabolic differences can have important effects on the validity of extrapolating from animals to man if, for example, the actual carcinogen is a metabolite of the administered chemical and the animals tested differ markedly from humans in their production of that metabolite. A related point is that the actual dose of carcinogen reaching the affected tissue or organ is usually not known; thus, dose-response information, of necessity, is based on administered dose and not tissue dose. Although data of these types would certainly improve the basis for extrapolating from high to low doses and from one species to another, they are difficult to acquire and often unavailable.

Regulators are interested in doses to which humans might be exposed, and such doses usually are much lower than those administered in animal studies. Therefore, dose-response assessment often requires extrapolating an expected response curve over a wide range of doses from one or two actual data points. In addition, differences in size and metabolic rates between man and laboratory animals require that doses used experimentally be converted to reflect these differences.

Low-Dose Extrapolation

One may extrapolate to low doses by fitting a mathematical model to animal dose-response data and using the model to predict risks at lower doses corresponding to those experienced by humans. At present, the true shape of the dose-response curve at doses several orders of magnitude below the observation range cannot be determined experimentally. Even the largest study on record—the ED_{01} study involving 24,000 animals—was designed only to measure the dose corresponding to a 1% increase in tumor incidence. However, regulatory agencies are often concerned about much lower risks (1 in 100,000 to 1

in 1,000). Several methods have been developed to extrapolate from high doses to low doses that would correspond to risk of such magnitudes. A difficulty with low-dose extrapolation is that a number of the extrapolation methods fit the data from animal experiments reasonably well, and it is impossible to distinguish their validity on the basis of goodness of fit. (From a mathematical point of view, distinguishing among these models on the basis of their fit with experimental data would require an extremely large experiment; from a practical point of view, it is probably impossible). As Figure 1-2 shows, the dose-response curves derived with different models to diverge below the experimental doses and may diverge substantially in the dose range of interest to regulators. Thus, low-dose extrapolation must be more than a curve fitting exercise, and considerations of biological plausibility must be taken into account.

Although the five models shown in Figure 1-2 may fit experimental data equally well, they are not equally plausible biologically. Most persons in the field would agree that the supralinear model can be disregarded, because it is very difficult to conceive of a biologic mechanism that would give rise to this type of low-dose response. The threshold model is based on the assumption that, below a particular dose (the "threshold" dose of a given carcinogen) there is no adverse effect. This concept is plausible, but not now confirmable. The ED_{01} study showed an apparent threshold for bladder cancers caused by 2-acetylaminofluorene; when the data were replotted on a scale giving greater resolution (OTA, 1981), the number of bladder tumors consistently increased with dose, even at the lowest doses, and no threshold was detected. Another aspect of the debate over thresholds for inducing carcinogenic effects is the argument that agents that act through genotoxic mechanisms are not likely to have a threshold, whereas agents whose effects are mediated by epigenetic mechanisms are possibly more likely to have a threshold. The latter argument is also currently open to scientific challenge. Finally, apparent thresholds observable in animal bioassays cannot be equated with thresholds for entire populations. Even if a threshold exists for individuals, a single threshold would probably not be applicable to the whole population.

Animal-to-Human Dose Extrapolation

In extrapolating from animals to humans, the doses used in bioassays must be adjusted to allow for differ

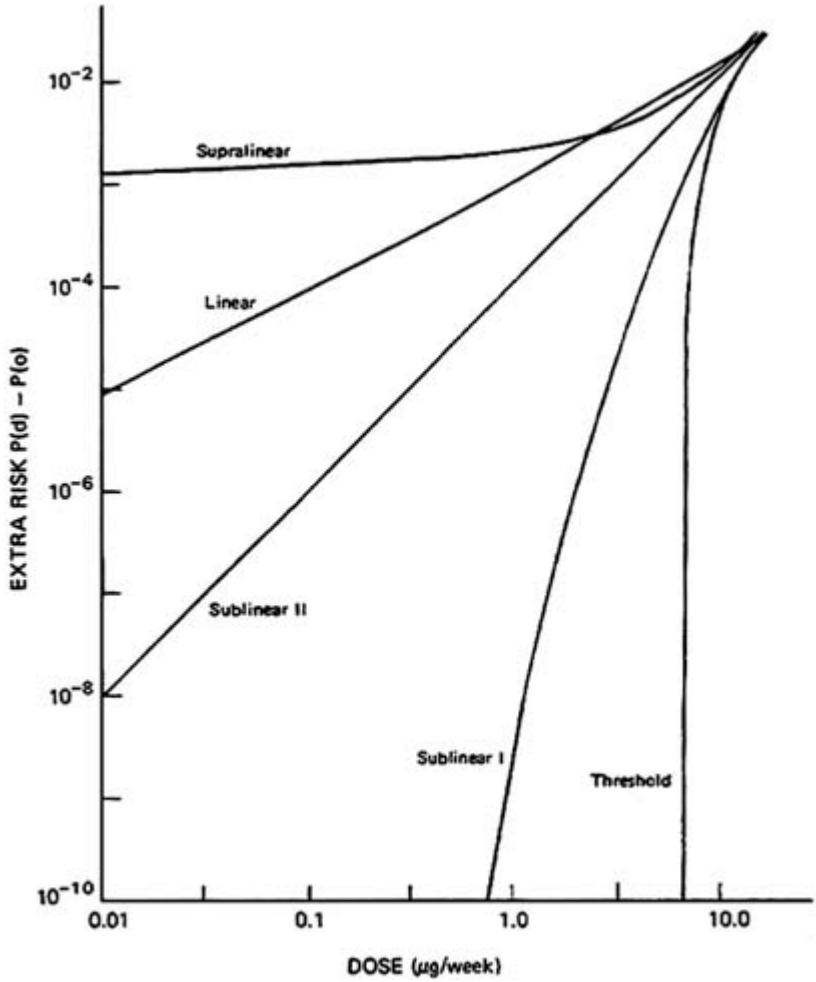

FIGURE 1-2 Results of alternative extrapolation models for the same experimental data. NOTE: Dose-response functions were developed (Crump, in press) for data from 1a benzopyrene carcinogenesis experiment with mice conducted by Lee and O'Neill (1971).

ences in size and metabolic rates. Several methods currently are used for this adjustment and assume that animal and human risks are equivalent when doses are measured as milligrams per kilogram per day, as milligrams per square meter of body surface area, as parts per million in air, diet, or water, or as milligrams per kilogram per lifetime. Although some methods for conversion are used more frequently than others, a scientific basis for choosing one over the other is not established.

Step 3. Exposure Assessment

The first task of an exposure assessment is the determination of the concentration of the chemical to which humans are exposed. This may be known from direct measurement, but more typically exposure data are incomplete and must be estimated. Models for estimating exposure can be complex, even in the case of structured activity, as occurs in the workplace. Exposure measurements made on a small group (e.g., workers in a particular industrial firm) are often applied to other segments of the worker population.

Exposure assessment in an occupational setting consists primarily of estimation of long-term airborne exposures in the workplace. However, because an agent may be present at various concentrations in diverse occupational settings, a census of exposures is difficult and costly to conduct. In the community environment, the ambient concentrations of chemicals to which people may be exposed can be estimated from emission rates only if the transport and conversion processes are known. Alternative engineering control options require different estimates of the reduction in exposure that may be achieved. For new chemicals with no measurement data at all, rough estimations of exposure are necessary. Some chemical agents are of concern because they are present in foods or may be absorbed when a consumer product is used. Assessments of exposure to such agents are complicated by variations in diet and personal habits among different groups in the population. Even when the amount of an agent in a food can be measured, differences in food storage practices, food preparation, and dietary frequency often lead to a wide variation in the amount of the agent that individuals ingest. Patterns of use affect exposure to many consumer products; for example, a solvent whose vapor is potentially toxic may be used outdoors or it may be used in a small, poorly ventilated room, where the concentration of vapor in the air is much higher.

Another important aspect of exposure assessment is the determination of which groups in the population may be exposed to a chemical agent; some groups may be especially susceptible to adverse health effects. Pregnant women, very young and very old people, and persons with impaired health may be particularly important in exposure assessment. The importance of exposures to a mixture of carcinogens is another factor that needs to be considered in assign human exposures. For example, exposure to cigarette smoke and asbestos gives an incidence of cancer that is much greater than anticipated from carcinogenicity data on each substance individually. Because data detecting such synergistic effects are often unavailable, they are often ignored or accounted for by the use of various safety factors.

Step 4. Risk Characterization

Risk characterization, the estimate of the magnitude of the public-health problem, involves no additional scientific knowledge or concepts. However, the exercise of judgment in the aggregation of population groups with varied sensitivity and different exposure may affect the estimate.

SCIENTIFIC AND POLICY JUDGMENTS IN RISK ASSESSMENT

The uncertainties inherent in risk assessment can be grouped in two general categories: missing or ambiguous information on a particular substance and gaps in current scientific theory. When scientific uncertainty is encountered in the risk assessment process, inferential bridges are needed to allow the process to continue. The Committee has defined the points in the risk assessment process where such inferences must be made as components. The judgments made by the scientist/risk assessor for each component of risk assessment often entail a choice among several scientifically plausible options; the Committee has designated these inference options.

Components of Risk Assessment

A list of components in carcinogenicity risk assessments was compiled by the Committee and is given below. This

list is not exhaustive or comprehensive, nor would all components listed be found in every risk assessment. The actual array of components in a particular risk assessment depends on a number of factors, including the types and extent of available data.

Hazard Identification
Epidemiologic Data

- What relative weights should be given to studies with differing results? For example, should positive results outweigh negative results if the studies that yield them are comparable? Should a study be weighted in accord with its statistical power?
- What relative weights should be given to results of different types of epidemiologic studies? For example, should the findings of a prospective study supersede those of a case-control study, or those of a case-control study those of an ecologic study?
- What statistical significance should be required for results to be considered positive?
- Does a study have special characteristics (such as the questionable appropriateness of the control group) that lead one to question the validity of its results?
- What is the significance of a positive finding in a study in which the route of exposure is different from that of a population at potential risk?
- Should evidence on different types of responses be weighted or combined (e.g., data on different tumor sites and data on benign versus malignant tumors)?

Animal-Bioassay Data

- What degree of confirmation of positive results should be necessary? Is a positive result from a single animal study sufficient, or should positive results from two or more animal studies be required? Should negative results be disregarded or given less weight?
- Should a study be weighted according to its quality and statistical power?
- How should evidence of different metabolic pathways or vastly different metabolic rates between animals and humans be factored into a risk assessment?
- How should the occurrence of rare tumors be treated? Should the appearance of rare tumors in a treated group be considered evidence of carcinogenicity even if the finding is not statistically significant?

- How should experimental-animal data be used when the exposure routes in experimental animals and humans are different?
- Should a dose-related increase in tumors be discounted when the tumors in question have high or extremely variable spontaneous rates?
- What statistical significance should be required for results to be considered positive?
- Does an experiment have special characteristics (e.g., the presence of carcinogenic contaminants in the test substance) that lead one to question the validity of its results?
- How should findings of tissue damage or other toxic effects be used in the interpretation of tumor data? Should evidence that tumors may have resulted from these effects be taken to mean that they would not be expected to occur at lower doses?
- Should benign and malignant lesions be counted equally?
- Into what categories should tumors be grouped for statistical purposes?
- Should only increases in the numbers of tumors be considered, or should a decrease in the latent period for tumor occurrence also be used as evidence of carcinogenicity?

Short-Term Test Data

- How much weight should be placed on the results of various short-term tests?
- What degree of confidence do short-term tests add to the results of animal bioassays in the evaluation of carcinogenic risks for humans?
- Should in vitro transformation tests be accorded more weight than bacterial mutagenicity tests in seeking evidence of a possible carcinogenic effect?
- What statistical significance should be required for results to be considered positive?
- How should different results of comparable tests be weighted? Should positive results be accorded greater weight than negative results?

Structural Similarity to Known Carcinogens

- What additional weight does structural similarity add to the results of animal bioassays in the evaluation of carcinogenic risks for humans?

General

- What is the overall weight of the evidence of carcinogenicity? (This determination must include a judgment of the quality of the data presented in the preceding sections.)

Dose-Response Assessment

Epidemiologic Data

- What dose-response models should be used to extrapolate from observed doses to relevant doses?
- Should dose-response relations be extrapolated according to best estimates or according to upper confidence limits?
- How should risk estimates be adjusted to account for a comparatively short follow-up period in an epidemiologic study?
- For what range of health effects should responses be tabulated? For example, should risk estimates be made only for specific types of cancer that are unequivocally related to exposure, or should they apply to all types of cancers?
- How should exposures to other carcinogens, such as cigarette smoke, be taken into consideration?
- How should one deal with different temporal exposure patterns in the study population and in the population for which risk estimates are required? For example, should one assume that lifetime risk is only a function of total dose, irrespective of whether the dose was received in early childhood or in old age? Should recent doses be weighted less than earlier doses?
- How should physiologic characteristics be factored into the dose-response relation? For example, is there something about the study group that distinguishes its response from that of the general population?

Animal-Bioassay Data

- What mathematical models should be used to extrapolate from experimental doses to human exposures?
- Should dose-response relations be extrapolated according to best estimates or according to upper confidence limits? If the latter, what confidence limits should be used?
- What factor should be used for interspecies conversion of dose from animals to humans?

- How should information on comparative metabolic processes and rates in experimental animals and humans be used?
- If data are available on more than one nonhuman species or genetic strain, how should they be used? Should only data on the most sensitive species or strain be used to derive a dose-response function, or should the data be combined? If data on different species and strains are to be combined, how should this be accomplished?
- How should data on different types of tumors in a single study be combined? Should the assessment be based on the tumor type that was affected the most (in some sense) by the exposure? Should data on all tumor types that exhibit a statistically significant dose-related increase be used? If so, how? What interpretation should be given to statistically significant decreases in tumor incidence at specific sites?

Exposure Assessment*

- How should one extrapolate exposure measurements from a small segment of a population to the entire population?
- How should one predict dispersion of air pollutants into the atmosphere due to convection, wind currents, etc., or predict seepage rates of toxic chemicals into soils and groundwater?
- How should dietary habits and other variations in lifestyle, hobbies, and other human activity patterns be taken into account?
- Should point estimates or a distribution be used?
- How should differences in timing, duration, and age at first exposure be estimated?
- What is the proper unit of dose?
- How should one estimate the size and nature of the populations likely to be exposed?
- How should exposures of special risk groups, such as pregnant women and young children, be estimated?

* Current methods and approaches to exposure assessment appear to be medium- or route-specific. In contrast with hazard identification and dose-response assessment, exposure assessment has very few components that could be applicable to all media.

Risk Characterization

- What are the statistical uncertainties in estimating the extent of health effects? How are these uncertainties to be computed and presented?
- What are the biologic uncertainties in estimating the extent of health effects? What is their origin? How will they be estimated? What effect do they have on quantitative estimates? How will the uncertainties be described to agency decision-makers?
- Which dose-response assessments and exposure assessments should be used?
- Which population groups should be the primary targets for protection, and which provide the most meaningful expression of the health risk?

The Interplay of Science and Policy in Risk Assessment

A key premise of the proponents of institutional separation of risk assessment is that removal of risk assessment from the regulatory agencies will result in a clear demarcation of the science and policy aspects of regulatory decision-making. However, policy considerations inevitably affect, and perhaps determine, some of the choices among the inference options. To examine the types of judgments required in risk assessment, the Committee has analyzed several components and the inference options for each.

Hazard Identification

The Committee has identified 25 components in hazard identification. These components differ in a number of ways. However, two major differences germane to the question considered here are the degree of scientific uncertainty encountered in each and the effect of choosing different inference options on the outcome of the risk assessment. Consider the following examples.

One component of risk assessment is the decision as to whether to use experimental animal data to infer risks to humans. Although data from studies of rats and mice may not always be predictive of adverse health effects in humans, the scientific validity of this approach is widely accepted. The use of positive animal data is the more conservative choice for this component. The use of

negative animal data to determine the absence of carcinogenic risk is less conservative, especially when the sensitivity of the assay is low. (The Committee uses the term conservative with appropriate modifiers to describe the degree to which a particular inference option for components in hazard identification will increase the likelihood that a substance will be judged to be a significant hazard to human health).

A component about which there is considerably more scientific uncertainty than the preceding example is the question of whether to count all types of benign tumors as evidence of carcinogenicity. Some benign tumors probably can progress to malignant lesions and some probably do not. The judgment that benign tumors and malignant tumors should be counted equally will affect tumor incidence and may influence the yes-no determination in hazard identification, and it can also affect the dose-response relation by increasing incidence at the doses tested. Thus, counting benign tumors is often the more conservative approach.

The examples just given differ in the degree to which scientific understanding can inform the judgments to be made. They are similar, however, in that for each, the available inference options differ in conservatism. For many components, this difference in degree of conservatism among plausible inference options is not as clear as in the preceding examples and depends on the data available on a given substance. For example, the decision to combine incidences for all tumor types and calculate an overall tumor incidence can influence the final yes-no decision in hazard identification. However, in this case, whether such a choice is more conservative than not combining incidences depends on the incidences for each tumor type in test and control animals. If the incidence in control animals is slightly below the incidences in test animals for all tumor types and individual differences are not statistically significant, combining all tumor types would be more conservative. However, if incidences show no consistent trend and differences are statistically significant for only one tumor type, combining the tumors would be less conservative.

Dose-Response Assessment

The Committee has identified 13 components of dose-response assessment. Two major components are high- to low-dose extrapolation and interspecies dose conversion.

In a recent NRC report on the health effects of nitrate, nitrite, and N-nitroso compounds (National Academy of Sciences, 1981), three extrapolation models (the one-hit model, the multistage model, and the multihit model) were used to estimate the dose of a carcinogenic nitrosamine (dimethylnitrosamine) needed to cause cancer in one of a million rats. The doses calculated were 0.03 parts per billion (one-hit), 0.04 ppb (multistage), and 2.7 ppb (multihit); that is, the risk estimate per unit of dose would be lower for the one-hit and multistage models than for the multihit model for this experiment.

Other judgments in dose-response assessment that will affect the final estimate include choice of the experimental data set (from among many that might be available) to be used to calculate the relation between dose and incidence of tumors (e.g., use of the most sensitive animal group will result in the most conservative estimate), choice of a scaling factor for conversion of doses in animals to humans (the risks calculated can vary by a factor of up to 35, depending on the method used), and the decision of whether to combine tumor types in determining incidence (as mentioned earlier, the decision to lump tumors might be more or less conservative than the decision not to combine incidences from different tumor types).

Exposure Assessment

Discussion of specific components in exposure assessment is complicated by the fact that current methods and approaches to exposure assessment appear to be medium- or route-specific. In contrast with hazard identification and dose-response assessment, exposure assessment has very few components that could be applicable to all media. For example, a model describing transport of a chemical through the atmosphere is necessarily quite different from a model describing transport through water or soil, whereas the use of a particular dose-response extrapolation model in dose-response assessment is independent of the medium or route of exposure. In any event, an assessor has several options available for estimating exposure to a particular agent in a particular medium, and these options will yield more or less conservative estimates of exposure. Among the options are different assumptions about the frequency and duration of human

exposure to an agent or medium, rates of intake or contact, and rates of absorption.

Risk Characterization

The final expressions of risk derived in this step will be used by the regulatory decision-maker when health risks are weighed against other societal costs and benefits to determine an appropriate action. Little guidance is available on how to express uncertainties in the underlying data and on which dose-response assessments and exposure assessments should be combined to give a final estimate of possible risk.

Basis for Selecting Inference Options

The Committee has presented some of the more familiar, and possibly more controversial, components of risk assessment. A review of the list of components reveals that many components lack definitive scientific answers, that the degree of scientific consensus concerning the best answer varies (some are more controversial among scientists than others), and that the inference options available for each component differ in their degree of conservatism. The choices encountered in risk assessment rest, to various degrees, on a mixture of scientific fact and consensus, on informed scientific judgment, and on policy determinations (the appropriate degree of conservatism).

That a scientist makes the choices does not render the judgments devoid of policy implications. Scientists differ in their opinions of the validity of various options, even if they are not consciously choosing to be more or less conservative. In considering whether to use data from the most sensitive experimental animals for risk assessment, a scientist may be influenced by the species, strains, and gender of the animals tested, the characteristics of the tumor, and the conditions of the experiment. A scientist's weighting of these variables may not easily be expressed explicitly, and the result is a mixture of fact, experience (often called intuition), and personal values that cannot be disentangled easily. As a result, the choice made may be perceived by the scientist as based primarily on informed scientific judgment. From a regulatory official's point of view, the same choice

may appear to be a value decision as to how conservative regulatory policy should be, given the lack of a decisive empirical basis for choice.

A risk assessor, in the absence of a clear indication based on science, could choose a particular approach (e.g., the use of an extrapolation model) solely on the basis of the degree to which it is conservative, i.e., on the basis of its policy implications. Furthermore, a desire to err on the side of overprotection of public health by increasing the estimate of risk could lead an assessor to choose the most conservative assumptions throughout the process for components on which science does not indicate a preferred choice. Such judgments made in risk assessment are designated risk assessment policy, that is, policy related to and subservient to the scientific content of the process, in contrast with policy invoked to guide risk management decisions, which has political, social, and economic determinants.

When inference options are chosen primarily on the basis of policy, risk management considerations (the desire to regulate or not to regulate) may influence the choices made by the assessors. The influence can be generic or ad hoc; i.e., assessments for all chemicals would consistently use the more or less conservative inference options, depending on the overall policy orientation of the agency ("generic"), or assessments would vary from chemical to chemical, with more conservative options being chosen for substances that the agency wishes to regulate and less conservative options being chosen for substances that the agency does not wish to regulate. (The desire to regulate or not would presumably stem from substance-specific economic and social considerations.) The possible influence of risk management considerations, whether real or perceived, on the policy choices made in risk assessment has led to reform proposals (reviewed later in this report) that would separate risk assessment activities from the regulatory agencies.

Table I-1 recapitulates the terms introduced in this discussion.

RISK ASSESSMENT IN PRACTICE

This section addresses past agency practices of risk assessment associated with efforts to regulate toxic substances.

TABLE I-1 Summary of Terms

Risk Assessment. Risk assessment is the qualitative or quantitative characterization of the potential health effects of particular substances on individuals or populations.
Risk Management. Risk management is the process of evaluating alternative regulatory options and selecting among them. A risk assessment may be one of the bases of risk management.
Steps. Risk assessments comprise many or all of the following steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization.
Components. Steps in risk assessment comprise many components—points in a risk assessment at which judgments must be made regarding the analytic approach to be taken.
Inference options. For many components, two or more inference options are available.
Risk Assessment Policy. Risk assessment policy consists of the analytic choices that must be made in the course of a risk assessment. Such choices are based on both scientific and policy considerations.

Risk Assessment and Regulatory Decision-Making

The regulatory process can be initiated in many ways. Each regulatory agency typically has jurisdiction over a large number of substances, but circumstances force an allocation of resources to a few at a time. The decision as to which substances to regulate is based, at least in part, on the degree of hazard. Thus, some notion of relative hazard (implicit or explicit, internally generated or imposed by outside groups) is necessary. Critics of federal regulation have contended that the agencies have not set their priorities sensibly. In general, agency risk assessments for priority-setting have been more informal, less systematic, and less visible than those for establishing regulatory controls.

Agenda-setting involves decisions about which substances should be selected (and often in what order) for more intense formal regulatory review. All programs face this problem, but it assumes different configurations: some programs cover a finite and known set of chemicals that must be reviewed, so the order of the regulatory reviews is the key question, and the primary job of the risk assessor is to help the agency implement a worst-first approach. For example, EPA's pesticides program has long had lists of suspect pesticide ingredients, and agency officials have had to decide which ones warrant formal consideration of cancellation or of new controls. An agency's agenda may also respond to private-sector initiatives (in the case of approval of new drugs or pesticides), conform to statutory directives, or react to new evidence of hazards previously unrecognized or thought to be less serious. This agenda formation phase, too, involves elements of risk assessment by the agency, the Congress, or private-sector entities; that is, there must be some assessment, however informal, that indicates reason for concern.

For many items on an agency's regulatory agenda, hazard identification alone will support a conclusion that a chemical presents little or no risk to human health and should be removed from regulatory consideration, at least until new data warrant renewed concern. If a chemical is found to be potentially dangerous in the hazard-identification step, it could then be taken through the steps of dose-response assessment, exposure assessment, and risk characterization. At any of these steps, the evaluation might indicate that a substance poses little or no risk and therefore can be removed from regulatory consideration until new data indicate a need for reevaluation.

Chemicals that are judged to present appreciable risks to health are candidates for regulatory action, and an agency will begin to develop options for regulating exposures. Regulatory options usually involve specific product or process changes and typically need to be based on extensive engineering and technical knowledge of the affected industry. Evaluation of the regulatory options includes recomputation of the predicted risk, in accord with altered expectations of exposure intensity or numbers of persons exposed.

Many of the activities of regulatory agencies do not conform to this sequential approach. However, regardless of the sequence of steps and the number of steps used to

determine whether regulatory action is warranted, risk assessment serves at least two major functions in regulatory decisions: first, it provides an initial assessment of risks, and, if the risk is judged to be important enough to warrant regulatory action, it is used to evaluate the effects of different regulatory options on exposure. In addition, it may be used to set priorities for regulatory consideration and for further toxicity testing.

These varied functions place different requirements on risk assessors, and a single risk assessment method may not be sufficient. A risk assessment to establish testing priorities may appropriately incorporate many worst-case assumptions if there are data gaps, because research should be directed at substances with the most crucial gaps; but such assumptions may be inappropriate for analyzing regulatory controls, particularly if the regulator must ensure that controls do not place undue strains on the economy. In establishing regulatory priorities, the same inference options should be chosen for all chemicals, because the main point of the analysis is to make useful risk comparisons so that agency resources will be used rationally. However, this approach, which may be reasonable for priority-setting, may have to yield to more sophisticated and detailed scientific arguments when a substance's commercial life is at stake and the agency's decision may be challenged in court. Furthermore, the available resources and the resulting analytic care devoted to a risk assessment for deciding regulatory policy are likely to be much greater for analyzing control actions for a single substance than for setting priorities.

The Agencies That Regulate

The approach to risk assessment varies considerably among the four federal agencies. Differences stem primarily from variations in agency structure and differences in statutory mandates and their interpretation.

Organizational Arrangements

The Food and Drug Administration (FDA) is a component of the Department of Health and Human Services, whose Secretary is the formal statutory delegate of the powers exercised by FDA. FDA is headed by a single official,

the Commissioner of Food and Drugs, who is appointed by and serves at the pleasure of the Secretary of the Department of Health and Human Services. It is organized in product-related bureaus, each of which employs its own scientists, technicians, compliance officers, and administrators. FDA has a long (75-year) and strong scientific tradition. According to a recent Office of Technology Assessment summary, FDA had taken or proposed action on 24 potential carcinogens by 1981.

Like FDA, the Environmental Protection Agency (EPA) is headed by a single official, but EPA's Administrator is appointed by the President subject to Senate confirmation. Also like FDA, EPA resembles a confederation of relatively discrete programs that are coordinated and overseen by a central management. The agency was established in 1970, but many of its programs (e.g., air and water pollution control and pesticide regulation) predate its formation and previously were housed in and administered by other departments. Other programs, such as those for toxic substances and hazardous waste, are rather new. EPA's research, policy evaluation, and, until recently, enforcement efforts were separated organizationally from the program offices that write regulations. EPA has had the widest experience with regulating carcinogens; as of 1981, it had acted on 56 chemicals in its clean-water program, 29 in its clean-air program, 18 in its pesticide program, and two in its drinking-water program.

The Occupational Safety and Health Administration (OSHA) is part of the Department of Labor. The agency's head is an Assistant Secretary of Labor, who requires Senate confirmation. Although FDA and EPA derive their scientific support largely from their own full-time employees, until the late 1970s OSHA relied on other agencies, primarily the National Institute of Occupational Safety and Health, an agency of the Department of Health and Human Services. This division reflects a conscious congressional choice in 1970 to place the health experts on whom OSHA was expected to rely in an outside environment believed more congenial to scientific inquiry and less vulnerable to political influence. As of 1981, 18 potential carcinogens had been acted on by OSHA.

The Consumer Product Safety Commission (CPSC) enforces five statutes, including the Consumer Product Safety Act and the Federal Hazardous Substances Act. Both empower CPSC to regulate unreasonable risks of injury from products used by consumers in the home, in schools, or in

recreation. The much smaller CPSC differs sharply from the other three agencies in two important respects: it does not have a single administrative head, but instead is governed by five Commissioner, who can make major regulatory decisions only by majority vote; and the Commissioners are appointed for fixed terms by the President with Senate confirmation. Before 1981, CPSC had acted on five potential carcinogens.

The four agencies have attempted to coordinate risk assessment activities in the past, most notably through the Interagency Regulatory Liaison Group (IRLG), which formed a work group on risk assessment to develop a guideline for assessing carcinogenic risks. Assisted by scientists from the National Cancer Institute and the National Institute for Environmental Health Sciences, it examined the various approaches used by the four agencies to evaluate evidence of carcinogenicity and to assess risk. The IRLG (1979a,b) then integrated and incorporated these evaluative procedures into a document, "Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks," which described the basis for evaluation of carcinogenic hazards identified through epidemiologic and experimental studies and the methods used for quantitative estimation of carcinogenic risk.

Regulatory Statutes*

Examination of the statutes that the four agencies administer reveals important differences in the standards that govern their decisions. The Office of Technology Assessment has summarized (Table 1-2) statutes that pertain to the regulation of carcinogenic chemicals. In particular, the statutes accord different weights to such criteria as risk, costs of control, and technical feasibility. In addition, different modes of regulation vary in their capacity to generate the scientific data necessary to perform comprehensive risk assessments.

Several laws require agencies to balance regulatory costs and benefits. Examples of balancing provisions are found in the Safe Drinking Water Act; the Federal Insecticide, Fungicide, and Rodenticide Act; the Toxic Substances

* This discussion draws heavily on the Office of Technology Assessment report, Technologies for Determining Cancer Risks from the Environment , 1981.

Control Act; and the section on fuel additives in the Clean Air Act. Under such provisions, a risk assessment can be used to express the nature and extent of public-health benefits to be attained through regulation.

Some regulatory programs involve the establishment of technology-based exposure controls. This approach is followed, for example, in portions of the clean-water program and the part of the hazardous-wastes program that deals with waste-incineration standards. In such programs, a risk assessment may be used to show the human exposure that corresponds to a specific degree of risk or to calculate the risk remaining after control technologies are put in place.

Some statutes mandate control techniques to reduce risks to zero whenever hazard is affirmed. Such techniques include outright bans of products, as envisioned in the Delaney clause in the Federal Food, Drug, and Cosmetic Act. In addition, if the concept of a threshold below which carcinogens pose no risk is not accepted, strict interpretations of ample margin of safety language in federal clean-air and clean-water legislation would require that exposures to carcinogenic pollutants be reduced to zero. The role of risk assessment in cases where mandatory control techniques must reduce risks to zero may be simply to affirm that a hazard exists.

The difference between programs that involve premarketing approval of substances and programs that operate through post hoc mechanisms, such as environmental emission limits, may have an important influence over the quality of risk assessments. The most important effect of this difference may lie in the fact that premarketing approval programs (such as those for pesticides, for new human drugs, and for new food additives) empower an agency to require the submission of sufficient data for a comprehensive risk assessment, whereas other programs tend to leave agencies to fend for themselves in the acquisition of necessary data.

There can be little question that differing statutory standards for decision affect the weight that agencies accord risk assessments. Like differences in the mode of regulation, they probably have affected the rigor and scope of many assessments. If risk is but one of several criteria that a regulator must consider or if data are expensive to obtain, it would not be surprising if an agency devoted less effort to risk assessment. However, the Committee has not discovered differences in existing statutes that should impede the adoption of uniform,

TABLE I-2 Public Laws Providing for the Regulation of Exposures to Carcinogens

Legislation (Agency)	Definition of toxics or hazards used for regulation of carcinogens	Degree of protection	Agents regulated as carcinogens (or proposed for regulation)	Basis of the legislation	Remarks
Federal Food, Drug and Cosmetic Act: (FDA)					
Food	Carcinogenicity *for additive* defined by Delaney Clause	No risk permitted, ban of additive	21 food additives and colors	Risk	
	Contaminants	"necessary for the protection of public health. . ." sec. 406 (346)	Three substances—aflatoxin, PCBs, nitrosamines	Balancing	
Drugs	Carcinogenicity is defined as a risk	Risks and benefits of drug are balanced.	Not determined	Balancing	
Cosmetics	"substance injurious under conditions of use prescribed."	Action taken on the basis that cosmetic is adulterated.	Not determined	Risk. No health claims are allowed for "cosmetics." If claims are made, cosmetic becomes a "drug."	
Occupational Safety and Health Act (OSHA)	Not defined in Act (but OSHA Generic Cancer Policy defines carcinogens on basis of animal test results or epidemiology.)	"adequately assures to the extent feasible that no employee will suffer material impairment of health or functional capacity. . ." sec. 6(b) (5)	20 substances	Technology (or balancing)	
Clean Air Act (EPA)					
Sec. 112 (stationary sources)	"an air pollutant. . . which . . . may cause, or contribute to, an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness." sec. 112(a) (1)	"an ample margin of safety to protect the public health. . ." sec. 112(b) (1) (B)	Asbestos, beryllium, mercury, vinyl chloride, benzene, radionuclides, and arsenic (an additional 24 substances are being considered)	Risk	Basis of the Airborne Carcinogen Policy

Sec. 202 (vehicles)	"air pollutant from any . . . new motor vehicles. . . . or engine, which . . . cause, or contribute to, air pollution which may reasonably be anticipated to endangor public health or welfare." sec. 202A(a) (1)	"standards which reflect the greatest degree of emission reduction achieveable through . . . technology . . . available. . ." sec. 202(b) (3)(a) (1)	Diesel particulates standard	Technology Sec. 202(b) (4) (B) includes a risk-risk test for deciding between pollutant that might result from control attempts.	Sec. 202(b) (4) (A) specifies that no pollution control device, system, or element shall be allowed if it presents an unreasonable risk to health, welfare or safety.
Sec. 211 (fuel additives)	Same as above (211(c) (1)).	Same as above (211(c) (2) (a)).	—	Balancing. Technology-based with consideration of costs, but health-based in requirement that standards provide ample margin of safety.	A cost-benefit comparison of compeling control technologies is required.
Clean Water Act (EPA) Sec. 307	Toxic pollutants listed in Committee Report 95-30 of House Committee on Public Works and Transportation. List from consent decree between EDF, NRDC, Citizens for Better Environment and EPA.	Defined by applying BAT economically achieveable (sec. 307(a) (2)), but effluent levels are to "provide(s) an ample margin of safety." (sec. 307(a) (4))	49 substances listed as carcinogens by CAG.	Technology	
Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Environmental Pesticide Control Act (EPA)	One which results in "unreasonable adverse effects on the environment or will involve unreasonable hazard to the survival of a species declared endangered. . ."	Not specified.	14 rebuttable presumptions against registrations either initiated or completed; nine pesticides voluntarily withdrawn from market.	Sec. 2(bb) Balancing: "unreasonable adverse effects. . ."	"Unreasonable adverse effects" means "unreasonable risk to man or the environment taking into account the economic, social, and environmental costs and benefits. . ."

Legislation (Agency)	Definition of toxics or hazards used for regulation of carcinogens	Degree of protection	Agents regulated as carcinogens (or proposed for regulation)	Basis of the legislation	Remarks
Resource Conservation and Recovery Act (EPA)	One which "may cause, or significantly contribute to an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness; or, pose a. . .hazard to human health or the environment. . ." sec. 1004(5) (A) (B)	"that necessary to protect human health and the environment. . ." sec. 3002-04	74 substances proposed for listing as hazardous wastes	Risk. The Administrator can order monitoring and set standards for sites.	
Safe Drinking Water Act (EPA)	"contaminant(s) which. . .may have an adverse effect on the health of persons." sec. 1401(1) (B)	"to the extent feasible. . .(taking costs into consideration). . ." sec. 1412(a) (2)	Trihalomethanes, chemicals formed by reactions between chlorine used as disinfectant and organic chemicals. Two pesticides and 2 metals classified as carcinogens by CAG, but regulated because of other toxicities.	Balancing	
Toxic Substances Control Act (EPA)					
Sec. 4 (to require testing)	substances which "may present an unreasonable risk of injury to health or the environment." sec. 4(a) (1) (A) (i)	Not specified.	Six chemicals used to make plastics pliable.	Balancing: "unreasonable risk."	
Sec. 6 (to regulate)	substances which "present(s) or will present an unreasonable risk of injury to health or the environment." sec. 6(a)	"to protect adequately against such risk using the least burdensome requirement" sec. 6(a)	PCBs regulated as directed by the law.	Balancing: "unreasonable risk."	

Sec. 7 (to commence civil action against imminent hazards)	"imminently hazardous chemical substance or mixture means a... substance or mixture which presents an imminent and unreasonable risk of serious or widespread injury to health or the environment."	Based on degree of protection in sec. 6			
Federal Hazardous Substances Act (CPSC)	"any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness ..." 15 USC sec.	"establish such reasonable variations or additional label requirements... necessary for the protection of public health and safety ..." 15 USC sec.		Risk	"Highly toxic" defined as capacity to cause death, thus toxicity may be limited to acute toxicity.
Consumer Product Safety Act (CPSC)	"products which present unreasonable risks of injury...in commerce," and "'risk of injury' means a risk of death, personal injury or serious or frequent injury." 15 USC sec. 2051 "imminently hazardous consumer product' means consumer product which presents imminent and unreasonable risk of death, serious illness or severe personal injury." 15 USC sec. 2061	"standard shall be reasonably necessary to prevent or reduce an unreasonable risk of injury." 15 USC sec. 2056	Five substances: asbestos, benzene, benzidine (and benzidine-based dyes and pigments), vinyl chloride, "tris"	Balancing: "unreasonable"	Standards are to be expressed, wherever feasible, as performance requirements.

SOURCE: Office of Technology Assessment, Technologies for Determining Cancer Risks from the Environment, 1981.

government-wide risk assessment guidelines. Indeed, it is not satisfied that there are legal bases for interagency differences in the performance—as distinct from the use—of risk assessment for chronic health hazards.

CONCLUSIONS

On the basis of a review of the nature and the policy context of risk assessment, the Committee has drawn the following general conclusions:

1. Risk assessment is only one aspect of the process of regulatory control of hazardous substances. Therefore, improvements in risk assessment methods cannot be assumed to eliminate controversy over federal risk management decisions.

   Restrictive regulation has seemed onerous to manufacturers, distributors, and users of products judged useful and valuable; conversely, inaction and delay with respect to regulatory proceedings have appeared callous and irresponsible to others. These dissatisfactions have been manifested in many ways, including criticism of risk assessment processes. The Committee believes that much of this criticism is inappropriately directed and gives rise to an unrealistic expectation that modifying risk assessment procedures will result in regulatory decisions more acceptable to the critics. Certainly risk assessment can and should be improved, with salutary effects on the appropriateness of regulatory decisions. However, risk management, although it uses risk assessment, is driven by political, social, and economic forces, and regulatory decisions will continue to arouse controversy and conflict.
2. Risk assessment is an analytic process that is firmly based on scientific considerations, but it also requires judgments to be made when the available information is incomplete. These judgments inevitably draw on both scientific and policy considerations.

   The primary problem with risk assessment is that the information on which decisions must be based is usually inadequate. Because the decisions cannot wait, the gaps in information must be bridged by inference and belief, and these cannot be evaluated in the same way as facts. Improving the quality and comprehensiveness of knowledge is by far the most effective way to improve risk assess

ment, but some limitations are inherent and unresolvable, and inferences will always be required. Although we conclude that the mixing of science and policy in risk assessment cannot be eliminated, we believe that most of the intrusions of policy can be identified and that a major contribution to the integrity of the risk assessment process would be the development of a procedure to ensure that the judgments made in risk assessments, and the underlying rationale for such judgments, are made explicit.

3. Two kinds of policy can potentially affect risk assessment: that which is inherent in the assessment process itself and that which governs the selection of regulatory options. The latter, risk management policy, should not be allowed to control the former, risk assessment policy.

   Risk management policy, by its very nature, must entail value judgments related to public perceptions of risk and to information on risks, benefits, and costs of control strategies for each substance considered for regulation. Such information varies from substance to substance, so the judgments made in risk management must be case-specific. If such case-specific considerations as a substance's economic importance, which are appropriate to risk management, influence the judgments made in the risk assessment process, the integrity of the risk assessment process will be seriously undermined. Even the perception that risk management considerations are influencing the conduct of risk assessment in an important way will cause the assessment and regulatory decisions based on them to lack credibility.

4. Risk assessment suffers from the current absence of a mechanism for addressing generic issues in isolation from specific risk management decisions.

   Although the practice of risk assessment has progressed in recent years, there is currently no mechanism for stimulating and monitoring advances on generic questions in relevant scientific fields or for the timely dissemination of such information to risk assessors.

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II

Inference Guidelines for Risk Assessment

INTRODUCTION AND DEFINITIONS

An inference guideline* is an explicit statement of a predetermined choice among the options that arise in inferring human risk from data that are not fully adequate or not drawn directly from human experience. A guideline might, for example, specify the mathematical model to be used to estimate the effects of exposure at low doses from observations based on higher doses. The most important feature of guideline use is that it changes the risk assessment process from one in which inference options are selected on a substance-by-substance basis to one in which they are selected once and thereafter

* The Committee hopes to avoid any misunderstanding resulting from its use of the terms inference guideline and guideline (used for brevity in lieu of inference guideline). This terminology is potentially confusing, because guidelines can be understood as codified principles addressed to a particular subject matter, risk assessment, or as describing the legal weight of any codified standards or principles. For the Committee, it has the former meaning. Inference guidelines are the principles followed by risk assessors in interpreting and reaching judgments based on scientific data. (Thus, our inference guidelines are distinct from the standards for toxicologic and other testing standards that many regulatory agencies and scientific bodies have adopted to govern, or at least influence, the generation of data later used in risk assessment.)

For many lawyers, the term guideline connotes the weight to be given to any set of codified principles, not

applied to an entire series of chemicals. In the absence of guidelines, assessors may well select the same inference options for substance after substance in a given agency program, and a common set of inference options may emerge, in common law fashion, from their consistent application in the program. But even the continued use of the same set of inference options over time does not necessarily imply that the assessors would make the same choices for every substance. Furthermore, outsiders would have no way of knowing what the common set is. In contrast, the use of guidelines makes more evident the generic choice of inference options, which we have seen in Chapter I, is based on both scientific and risk assessment policy considerations.

HISTORY OF THE USE OF GUIDELINES

SAFETY EVALUATION GUIDELINES FOR EFFECTS OTHER THAN CANCER

The development and use of guidelines by a regulatory agency first became of major importance after Congress

only those addressed to risk assessment, in legal proceedings. The Food and Drug Administration, for example, has defined a guideline as an official pronouncement of the agency describing a procedure that satisfies legal requirements, but is not mandated by law. A more complete treatment of the distinction between binding regulations and other formal agency pronouncements appears in the section of this chapter entitled "Degree to Which Guidelines May Be Binding on an Agency and a Regulated Party."

The Committee has used the term guideline to describe the principles by which risk assessments are to be performed, because that is the term Congress used in the legislation that authorized this study. The Committee was asked to consider the feasibility of establishing uniform "risk assessment guidelines." There is no evidence that Congress was aware of the different meanings of the term. It obviously was seeking advice about the intellectual and scientific bases for codified principles for risk assessment, not the appropriate legal form for their adoption. Faced with possible confusion no matter which terminology it chose, the Committee has retained the language that Congress itself used to describe our inquiry.

enacted amendments to the Federal Food, Drug, and Cosmetics Act in the 1950s and early 1960s. These laws, as applied to noncarcinogenic agents, required that food additives, color additives, drugs for animals, and pesticides be shown to be safe under their intended conditions of use before premarket approval by the Food and Drug Administration (FDA). The agency developed guidelines to provide a systematic way to deal with the legal requirements embodied in the amendments. Although guidelines for the conduct of various types of toxicity tests received greatest notice, some attention was given to the problem of data interpretation for inferring human risk. For example, a 1959 publication written by several members of the FDA Division of Pharmacology, Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics, is devoted primarily to toxicity testing methods, but contains one chapter called "Some Interpretative Problems in Evaluating the Safety of Food Additives" (Lehman et al., 1959). Although that publication, which served as a guide for both FDA and the regulated industry for at least a decade, was never published as a regulation, it was widely accepted by affected industrial concerns.

In all cases except that of carcinogens, establishment of acceptable intakes was accomplished by applying safety factors to experimentally derived no-observed-effect exposures. Testing involved mostly the use of acute and subchronic (90-day) animal tests, although some long-term tests were required. The use of safety factors to establish acceptable intakes was also recommended by the Food Protection Committee of the National Research Council (NRC/NAS, 1970) and adopted by the Joint Food and Agricultural Organization and World Health Organization Expert Committees on Food Additives (1972) and Pesticide Residues (1965). This approach continues to be used for noncarcinogenic food additives and pesticides and, in slightly modified form, to define acceptable exposures to occupational and various environmental pollutants.

These methods of assigning acceptable limits of exposure imply that the application of safety factors of various magnitudes to experimentally derived no-observed-effect exposures will ensure low risk. The acceptable exposure, whether expressed as an acceptable daily intake for a food additive or as a permissible exposure limit for an occupational agent, is derived by imposing untested assumptions (e.g., about the likely nature of dose-response relations at low doses) and by drawing inferences from sparse data. Safety evaluation schemes may therefore

be classified as a set of guidelines that emphasize testing methods heavily and that afford methods of inference only scant attention.

Recent efforts have dealt more directly with developing guidelines for risk assessment of noncarcinogenic effects. The Environmental Protection Agency (EPA) has proposed guidelines for chemical mutagenesis (EPA, 1980a) and has collected public comments on them, but has yet to publish a final rule. In addition, the agency cosponsored two conferences with Oak Ridge National Laboratory on risk assessment methods for reproductive and teratogenic effects; the proceedings of the conferences have been published (ORNL/EPA, 1982). The Interagency Regulatory Liaison Group began to develop guidelines for risk assessment of reproductive and teratogenic effects, but the effort ceased with the disbanding of the group in 1981. The March of Dimes Birth Defects Foundation (1981) has published the proceedings of a conference dealing with guidelines for studies of human populations exposed to mutagenic and reproductive hazards. Despite the increasing interest in noncarcinogenic effects, methods of estimating the risk of these effects have not been the subject of major public and scientific debate; attention has been devoted mainly to carcinogenic risk assessment. Much more critical review of the inferential methods for assigning risks to noncarcinogenic agents is warranted.

Guidelines for Carcinogenic Risk

Until the late 1950s, few agents, either chemical or physical, had been regulated in this country on the basis of their carcinogenic action. One important regulated agent was ionizing radiation. Permissible exposures to radiation were set in a manner similar to that for noncarcinogenic agents, by application of safety factors applied to specified exposures. In the debate over health effects of radioactive fallout from atomic weapons tests in the 1950s, evidence to support a nonthreshold theory for cancer induction emerged. Evidence was also accumulated to indicate that the nonthreshold theory might be applicable to chemical carcinogens. It was in this context that Congress enacted statutes* in the 1950s and early

* The enactment of these statutes did not necessarily bring a unique new concept to FDA. In the early 1950s,

1960s that required FDA to ban the use of food and color additives shown to be carcinogenic. The assumption, which differed from that underlying safety evaluation of noncarcinogens, was that no exposure could be presumed safe. Thus, a full risk assessment scheme was not needed for carcinogens. The process stopped at hazard identification.

Many factors contributed to the later use of dose-response assessment, exposure assessment, and risk characterization to determine quantitative estimates of risk. One of these may have been the growing perception during the 1960s and 1970s that many kinds of risk could not be eliminated completely without unacceptable social and economic consequences. New laws reflecting this belief were enacted, and some agencies were required to balance the risk posed by carcinogenic agents against their perceived benefits. Quantitative risk assessment was the system developed to estimate the risk side of the balance. Over a period of 2 decades, various expert committees sponsored by government agencies and other organizations published numerous reports dealing with carcinogenicity evaluation. Most of these were state-of-the art reports on aspects of carcinogenicity inference, and many suggested guidelines for hazard identification. More recent reports have dealt explicitly with quantitative risk assessment. The impetus for producing these reports was probably a belief in the federal research and regulatory communities that some scientific principles related to carcinogenicity data evaluation had to be continually reexamined and reaffirmed. This belief pervaded the public-health establishment not only in the United States, but also in other countries and in the United Nations.

The following discussion examines efforts to develop and apply guidelines for the evaluation of carcinogenicity data by the federal regulatory agencies and the International Agency for Research on Cancer over the last decade—efforts that developed out of 2 decades of scientific consensus-building.

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before their enactment, the agency had prohibited three food additives on the grounds that they were found to be carcinogenic in test animals.

International Agency for Research on Cancer (IARC)

In 1971, the International Agency for Research on Cancer (IARC), an agency of the World Health Organization, began publication of a series of monographs on known and suspected carcinogens. These monographs are prepared by international groups of experts assembled by IARC, who critically review pertinent literature and draw conclusions regarding the carcinogenicity of various substances. The results of IARC reviews and evaluations are widely accepted. The guidelines used for evaluation by the IARC expert committees are set forth in the monographs. They are expressed in very general terms and are related to only six components of hazard identification, completely covered in six pages of text. A major feature of the guidelines is the presentation of criteria that classify the evidence of suspected carcinogens as sufficient or limited. The IARC allows the expert committees considerable latitude to evaluate many inference options on a case-by-case basis, although the agency appears to insist on adherence to the few stated guidelines.

Food and Drug Administration

The 1958 Food Additives Amendment to the Food, Drug, and Cosmetics Act prohibited the use of food additives found to be carcinogenic. The law was also interpreted as prohibiting FDA approval of any drug, for use in animals produced for human food, that had been shown to cause cancer. In 1962, by congressional amendment, FDA was permitted to approve the use of a carcinogenic animal drug if the agency was convinced that no residue of a drug would be found in edible tissues of the treated animals. Congress specified that FDA was to prescribe the analytic methods for verifying the absence of residues. This directive proved to be unworkable, for two reasons: progress in analytic quickly became obsolete and improved detection methods showed that no drug administered to animals is ever entirely absent from animal tissues. The problem of enforcing the 1962 amendment was highlighted in the early 1970s, when diethylstilbestrol residues were discovered in beef liver with highly sensitive, but as yet unapproved, analytic methods.

In an attempt to provide a consistent and predictable procedure for approving methods to search for drug resi

dues, FDA proposed sensitivity-of-method guidelines in the form of regulations (FDA, 1973, 1977, 1979b). Rather than gear criteria to an analytic technique, the agency defined its standards in terms of risk. It proposed that any assay approved for controlling a carcinogenic drug must be capable of measuring residues that present more than an insignificant risk of cancer, and specified a 10-6 lifetime risk of cancer as a quantitative criterion of insignificance. If a drug sponsor could provide a detection method capable of measuring residues posing a risk of this magnitude or greater, FDA would ignore residues that could not be detected with this method. Thus, FDA found guidelines for quantitative estimation of risk necessary. FDA's sensitivity-of-method guidelines are unique in several ways. They address a narrow though complex set of issues encountered in regulating a single class of products, animal drugs. Although they deal to a large extent with testing, they were the first to address quantitative risk assessment methods, listing assumptions for dose-response assessment, exposure assessment, and risk characterization. And they are the only guidelines that attempt to establish a definition of significant risk. The guidelines have yet to be adopted, a decade after they were first proposed, but the agency has applied the methods of quantitative risk assessment embodied in the sensitivity-of-method document in connection with the regulation not only of animal drugs, but also of food contaminants, such as aflatoxin (FDA, 1979a) and trace constituents of some additives (FDA, 1982b). The sensitivity-of-method guidelines were proposed as regulations, as were the cancer guidelines of the Occupational Safety and Health Administration (OSHA). In both cases, regulation engendered substantial controversy. The major debate over the sensitivity-of-method guidelines has dealt not so much with risk assessment or the definition of significant risk as with the amount and cost of testing that FDA would require from industry before product approval.

Environmental Protection Agency

During the early to middle 1970s, EPA initiated actions to prohibit or restrict the use of several pesticides. The agency lacked internal procedures for assessing carcinogenic risk and relied heavily on the judgment of scientists outside EPA. Attorneys for EPA, in summar

izing the testimony of their expert witnesses during administrative hearings on actions against the pesticides, set forth several statements that, in the legal brief, were referred to as cancer principles (EPA, 1972, 1975). They conveyed the idea that the only acceptable degree of regulation would be a total ban on exposures. The principles, perceived as EPA's cancer policy, incurred wide criticism from the scientific community, the private sector, and Congress. The impracticability of achieving zero risk on a broad scale for a large number of economically important chemicals became increasingly apparent. In response to this new perception, and perhaps out of a desire to avoid misunderstanding of its cancer policy, the EPA became the first agency to adopt formal guidelines embracing a two-step process of risk assessment (EPA, 1976). The first step is a determination of whether a particular substance constitutes a cancer risk (hazard identification). The second step is a determination of what regulatory action, if any, should be taken to reduce the risk. As part of the second step, the agency explicitly endorses the use of quantitative risk assessment as the means of determining the magnitude of the likely impact of a potential human carcinogen on public health. These guidelines were not published as regulations and enjoy fairly wide acceptance from most interested parties. As stated in the preface to the guidelines, they were published to improve agency procedures, to provide public notice of the approach that EPA would take, and to stimulate commentary from all sources on that approach. The guidelines were probably more important as a statement of a novel approach to risk assessment than for their content. They are quite general, cover less than a page of Federal Register text, and address only a few components of hazard identification, dose-response assessment, exposure assessment, and risk characterization. More detailed guidelines that specify assumptions for the choice of extrapolation models, scaling factors, and other elements of dose-response assessment were published in 1980 by program offices in EPA (EPA, 1980b). These rely in part on the Interagency Regulatory Liaison Group (IRLG) guidelines (IRLG, 1979a) and are currently undergoing review.

Occupational Safety and Health Administration

In 1977, OSHA published guidelines in a proposed regulation, "Identification, Classification, and Regulation of

Toxic Substances Posing a Potential Occupational Risk of Cancer" (OSHA, 1977); after extensive administrative hearings, it published a final rule in 1980 (OSHA, 1980). The guidelines proved to be highly controversial, and the hearings were marked by vigorous debate on almost every component of risk assessment covered by the guidelines.

The OSHA rule, written by agency staff, was a detailed scientific and regulatory document that took several hundred pages of Federal Register text and addressed almost every component of hazard identification. The final rule did not address exposure assessment and rejected the use of dose-response assessment for any regulatory purpose except priority-setting. The main purposes of the guidelines, as stated in the preface, were to streamline the process of risk assessment, to speed up regulation, and to reduce the workload of agency staff. Another purpose was to foster continuity of approach, even in the face of changes of policy-makers. OSHA staff perceived that the case-by-case approach to risk assessment was long and time-consuming, because the same controversial questions had to be argued each time a chemical was under consideration for regulation. The agency believed that the generic approach to risk assessment would reduce debate on these questions; the controversial issues could be decided once, incorporated into guidelines, and applied to all chemicals. For reasons of efficiency, the guidelines were written in language that permitted little deviation from the judgments embodied in them. Because they were written as regulations, regulated parties were required to abide by them. The agency has not used the rule as a basis for any published scientific assessment of carcinogenic hazard. It was revised in 1981 (OSHA, 1981) to accommodate the Supreme Court's ruling on benzene, which required that OSHA make a finding that the risk to workers in the absence of regulation was significant and would be reduced by the proposed standard. But this change and additional amendments were recently withdrawn, and the entire policy is under reconsideration (OSHA, 1982).

Consumer Product Safety Commission

The Consumer Product Safety Commission (CPSC) proposed cancer guidelines dealing mainly with hazard identification (CPSC, 1978). Ten components related to that step were addressed in several pages of Federal Register text.

Some minor attention was given to exposure assessment and dose-response assessment, for priority-setting purposes only. The rationale for publishing the guidelines, as stated in the preface of that document, was to establish CPSC's general principles and to solicit comments on them, to assist the general public and the regulated industries in understanding standards that CPSC would apply and regulatory actions that it was likely to take, and to set forth its approach to some issues that tended to recur in each case. The guidelines had no regulatory status; they were a statement of selected inference options to which the agency would adhere. The CPSC guidelines were never used; they were challenged in court, and the court ruled that CPSC had promulgated them illegally inasmuch as they were adopted without an opportunity for public comment. Furthermore, at that time CPSC had decided to rely on the guidelines of IRLG.

Interagency Regulatory Liaison Group

The four agencies represented in IRLG undertook the task of developing guidelines to "ensure that the regulatory agencies evaluate carcinogenic risk consistently." In 1979, after an 18-month interagency effort, IRLG published a report, "Scientific Bases for Identification of Potential Carcinogens and Estimation of Risk." The report was prepared by personnel of CPSC, EPA, FDA, and OSHA, with the assistance of senior scientists from the National Cancer Institute and the National Institute of Environmental Health Sciences. It was published in a scientific journal (IRLG, 1979b) and in the Federal Register (IRLG, 1979a); IRLG requested public comment in the Federal Register. The IRLG report was said to represent an interagency consensus on the scientific aspects of carcinogenic risk assessment.* It was the most comprehensive set of guidelines that had been developed for agency use, addressing most components of hazard identification and dose-response assessment with some general discussion of

* Because rule-making was under way in connection with its cancer policy, OSHA declined to participate in the IRLG notice and comment procedure. After the report was completed, the Food Safety Quality Service of the U.S. Department of Agriculture joined IRLG and participated in the notice and comment.

exposure assessment and risk characterization; it had, however, no official legal status. The report was noteworthy, in that it constituted the first evidence that all the federal regulatory agencies agreed on the inference options applicable to the identification of carcinogenic hazards and measurement of risks. The document made clear, however, that not all the agencies were bound to conduct quantitative assessments; it stated only that, if such assessments were to be conducted, they would be conducted uniformly. This language was probably a concession to OSHA's view, as expressed in its cancer policy, that quantitative risk assessment was to play no more than a priority-setting role in that agency's regulatory activities. Almost immediately after its publication, the IRLG report was adopted by the President's Regulatory Council and incorporated as the scientific basis of the Council's government-wide statement on regulation of chemical carcinogens. The Council viewed the IRLG guidelines as a major step in reducing inconsistency, duplication of effort, and lack of coordination among agencies in carcinogenic risk assessment (Regulatory Council, 1979).

The scientific aspects of the final OSHA cancer policy, which was written to allow less latitude in the choice of inference options, were, nevertheless, in general agreement with the IRLG guidelines. CPSC and EPA stated that they relied on the IRLG document, but the degree to which they rely on it today is not clear. FDA has made no statement other than that associated with the document's initial publication; in fact, in a recent proposal concerning the application of risk assessment to a class of trace constituents of additives, FDA did not even cite the IRLG document as a reference (FDA, 1982b). Although IRLG received a great deal of public comment on the guidelines, no report of the agencies' review of these comments has appeared. In fact, the document was heavily criticized by industry, because it was published in its final form and adopted before the comments could be analyzed and revisions incorporated. The Reagan Administration has officially disbanded the entire IRLG effort, so it is unlikely that review of the public comments will ever occur.

Although the IRLG charter was not renewed, a similar group has been established, but one that is coordinated by the White House Office of Science and Technology Policy. This group has prepared a draft document on the scientific basis of risk assessment and has distributed

it for comment (OSTP, 1982). The group anticipates that this document may serve as a reference point for later development of general guidelines for the agencies.

VARIATION IN THE FORM OF GUIDELINES

Comprehensiveness

Guidelines developed by agencies in the past have varied in the extent to which they have addressed each of the steps of risk assessment. IARC's guidelines address only hazard identification; OSHA's guidelines (1980) dealt mainly with hazard identification, with some discussion of dose-response assessment and none of exposure assessment and risk characterization; and IRLG's guidelines focused in detail on hazard identification and dose-response assessment, with some discussion of exposure assessment and risk characterization.

Guidelines also have varied in the extent to which they have addressed the components of the risk assessment steps. IARC's guidelines address a small number of components. Study of the latest IARC monograph (1982) reveals only six selected options that deal with inference of risk: treatment of benign versus malignant tumors, the choice of statistical methods for application of data from animal studies, the relevance of negative results of epidemiologic studies, the evaluation of tumors that occur spontaneously, the utility of short-term tests, and the overall weighting of evidence. The OSHA (1980) and IRLG documents, in contrast, each discussed and embraced over 20 selected options dealing with hazard identification.

Extent of Detail

Guidelines have differed not only in their comprehensiveness, but also in the detail with which they have treated specific components of risk assessment. When the content of a guideline is detailed, the assessor is presented with more complete information than would be available from a more general guideline. For example, the statement in IARC's guidelines on benign tumors is general, compared with that in the IRLG guidelines. IARC concludes briefly:

> If a substance is found to induce only benign tumors in experimental animals, it should be

suspected of being a carcinogen and requires further investigation.

The IRLG document made a similar statement, but in addition elaborated on several issues relevant to the evaluation of benign tumors that are not mentioned by IARC—e.g., evaluation of tumor incidence when both benign and malignant tumors are present; a listing of tumor types commonly observed as benign in test animals, but known to progress to frank malignant stages; evaluation of the quality of a histologic examination that might be presented as evidence; and an illustrative example of the dependence of response on the genetic characteristics of the test animal. The additional material could have been used by an assessor, particularly one not familiar with the newest information on benign tumors, to ensure that a more thorough analysis of the relevant issues had been performed.

Flexibility

Detail can often be confused with inflexibility, and it is important to make a distinction between these characteristics. Certainly, detailed guidelines can be inflexible if the detail is designed to limit agency discretion, and thus public debate, on an issue that is subject to multiple scientific interpretations. However, detailed guidelines can have quite a different effect if their intent is to provide an assessor with background information that describes the complexity of an issue, with nuances that may influence particular judgments, or with examples of cases that are legitimate exceptions to the general rule.

As described in Chapter I, almost all components of risk assessment theoretically embrace one or more inference options. For example, in determining which dose-response curve to choose, the biologically plausible inference options may include the linear, multistage, sublinear, and threshold models. A guideline usually prefers one option, although some guidelines permit the selection of more than one or of all the options. The preferred inference option may be viewed as a default option, i.e., the option chosen on the basis of risk assessment policy that appears to be the best choice in the absence of data to the contrary. A guideline may be said to be flexible according to the degree to which it

allows the default option to be superseded by another inference option as a result of convincing scientific evidence.*

Comparison of IRLG's guidelines with OSHA's guidelines illustrates how comprehensive and detailed guidelines have varied in flexibility. On the issue of benign versus malignant tumors, IRLG's guideline stated:

> The induction of benign neoplasms would, therefore, be considered evidence of carcinogenic activity unless definitive evidence is provided that the test chemical is incapable of inducing malignant neoplasms.

The guideline did not attempt to define the type of definitive evidence that would be needed to demonstrate that a "test chemical is incapable of inducing malignant neoplasms." In contrast, OSHA created strict minimal criteria for acceptance of such evidence:

> (i) Benign tumors. Results based on the induction of benign or malignant tumors, or both, will be used to establish a qualitative inference of carcinogenic hazard to workers. Arguments that substances that induce benign tumors do not present a carcinogenic risk to workers will be considered only if evidence that meets the criteria set forth in 1990.144(e) is provided.
> Section 1990.144(e) stated:
> (e) Benign tumors. The Secretary will consider evidence that the substance subject to the rule-making proceeding is capable only of inducing benign tumors in human or experimental animals provided that the evidence for the specific substance meets the following criteria:
> Criteria. (i) Data are available from at least two well-conducted bioassays in each of two species of mammals (or from equivalent evidence in more than two species).

* Flexibility is also intimately related to the legal weight that the agency desires a guideline to have; the implications for flexibility of adopting guidelines under different legal authorities are reviewed in the next section.

> (ii) Each of the bioassays to be considered has been conducted for the full lifetime of the experimental animals.
> (iii) The relevant tissue slides are made available to OSHA or its designee and the diagnoses of the tumors as benign are made by at least one qualified pathologist who has personally examined each of the slides and who provides specific diagnostic criteria and descriptions; and
> (iv) All of the induced tumors must be shown to belong to a type which is known not to progress to malignancy or to be at a benign stage when observed. In the latter case, data must be presented to show that multiple sections of the affected organ(s) were adequately examined to search for invasion of the tumor cells into adjacent tissue, and that multiple sections of other organs were adequately examined to search for tumor metastases.

By leaving open the type of evidence needed to supersede the default option (benign tumors should be considered evidence of carcinogenic activity), IRLG allowed more flexibility than OSHA.

In no case did the IRLG guidelines attempt to restrict the type of evidence that would be needed for acceptance of alternative interpretations. In contrast, OSHA specified minimal criteria for acceptance of alternative interpretations on the issues of negative epidemiologic studies, proof of metabolic differences between animals and humans, and rejection of the use of data from testing at high doses. By invoking such criteria, OSHA attempted to limit the definition of acceptable interpretation and, in so doing, eliminate or reduce scientific debate on controversial issues in its rule-making proceedings.

IRLG also created flexibility by not choosing a default option, i.e., by citing a range of possible inference options to be used in a risk assessment. The statement on interspecies conversion factors illustrates this point:

> Several species-conversion factors should be considered in estimating risk levels for humans from data obtained in another species.

All OSHA guidelines were restricted to the choice of a single inference option.

Degree To Which Guidelines May Be Binding on An Agency and A Regulated Party

The guidelines developed by or for regulatory agencies may vary in their legal status and thus in their procedural implications. For example, OSHA's guidelines (1980) appeared as regulations formally published, after opportunity for public comment, in the Federal Register . In contrast, EPA's guidelines (1976), although eventually printed in the Federal Register, have never been officially subjected to public comment and do not purport to be regulations.

To appreciate the practical differences among the approaches that an agency might follow, it is useful to distinguish three types of administrative documents: regulations (or, synonymously, rules), established procedures (a term we have devised to refer to agency pronouncements that are in some contexts referred to as guidelines), and recommendations. There is no single authoritative definition of the latter two types of document. The discussion here is an attempt to reflect common understanding; it draws as well on the practice, but not the terminology of one agency, FDA (1982a).* An illustration will illuminate the practical differences among these three types of documents. Suppose that an agency decides to adopt, as one of its risk assessment guidelines, the default option that benign tumors should be aggregated with malignant tumors in determining whether a mammalian bioassay demonstrates that an agent causes cancer in the test species. This guideline could be adopted as a regulation, as what we term an established procedure, or simply as a recommendation. For internal purposes, it is not likely to matter which form the

* FDA officially recognizes three types of documents: binding regulations, guidelines, and recommendations. That terminology is potentially confusing here, because we have given guidelines a special meaning, connoting codified principles for risk assessment, that diverges from FDA's legal definition. The reader is referred to the footnote at the beginning of this chapter for a more complete treatment of this discrepancy. We have therefore coined the substitute phrase established procedures, to describe any standards of criteria for fulfilling a regulatory requirement that the agency commits itself to follow until they are formally revoked or revised.

agency's guideline takes. If the guideline is understood to represent prevailing agency policy, the agency's managers can assume that assessors will adhere to it in evaluating test data, regardless of its form. Important differences will be observed, however, in the guideline's impact on interested third parties.

If the guideline were adopted as a regulation, it would be reciprocally binding. Neither the agency nor any private party would be free to argue in a regulatory proceeding that benign and malignant tumors should never be aggregated or should not in a particular instance be aggregated; the agency's regulation would render such arguments legally irrelevant. It is precisely this effect of regulations—i.e., their treatment of previously contested (and in theory still contestable) issues as authoritatively resolved—that OSHA sought when it published its risk assessment guidelines as regulations.

If the guidelines were merely a recommendation, manufacturers of chemicals under evaluation would not be bound by it. They could argue, to the agency or in court, that benign tumors should never be aggregated with malignant tumors or that they should not be aggregated in a particular case. They might not convince the agency, but the agency could not lawfully refuse to consider their arguments or reject evidence supporting them, and they might convince a court that the agency guideline—i.e., its choice of inference options—is wrong generally or inapplicable in a particular case.

If the guideline were an established agency procedure, a private party could similarly argue that it is wrong generally or inapplicable to a particular case. An established procedure does not, therefore, preclude efforts by third parties to treat the benign-versus-malignant issue as an open question. The difference between a recommendation and an established procedure lies in the latter's effect on the agency itself. An agency can depart from a recommendation at any time. Under FDA's practice, however, it may not depart from an established procedure unless it has previously announced that it no longer regards the procedure as sound. In other words, such an established procedure is binding on the agency until formally revoked or changed, and third parties can rely on it and insist that the agency adhere to it.*

* The practical effects of the legal distinctions drawn here are possibly overdrawn. The flexibility accorded by

There is another important difference between regulations and established procedures or, indeed, recommendations. To adopt regulations that have the reciprocally binding effects described above, an agency must follow the procedures prescribed by the Administrative Procedure Act, or by its own statute, for rule-making. At a minimum, these procedures include publication of a proposal, an opportunity for the submission of public comments, and promulgation of a final document that discusses and responds to all significant comments. The process can be long and acrimonious, and that helps to explain why agencies sometimes choose not to adopt policies, particularly those addressing complex issues, in the form of regulations. The same process must be followed to effect changes in regulations once adopted, and that inhibits rapid response to changes in scientific understanding.

ARGUMENTS FOR AND AGAINST THE USE OF GUIDELINES

The advantages and disadvantages listed below constitute an inventory of arguments that have been brought forward by the proponents and critics of guidelines for risk assessment. In most cases, an argument is most convincing for guidelines of a particular form and content, rather than for guidelines in general. For these cases, the characteristics of guidelines that would support or refute an argument are indicated.

any set of guidelines depends as much on the language chosen as on the legal form in which they appear. Suppose that an agency's default option is: "Ordinarily benign and malignant tumors shall be equated and their sum used to determine the significance of observed effects, unless (a) new data suggest the inappropriateness of this practice generally, or (b) results from the test in question or other tests of the compound make aggregation inappropriate in the particular case." This text anticipates exceptions, and would not prevent either the agency or a third party from taking a different view about the meaning of a particular test, whether it appeared as a regulation or in some other form.

Advantages of Guideline Use

Separation of Risk Assessment from Risk Management

Proponents of guidelines argue that their use would help to separate risk assessment from other parts of the regulatory process. They contend that, when selected inference options are clearly delineated in a formal document, risk assessments will not likely be influenced to fit prior conclusions about regulation of a particular substance. The use of guidelines can also dispel the appearance of such influence when, in fact, there is none. Agencies can defend their assessments on the grounds that they always do them in the way set forth in the guidelines. Compared with reliance on the ad hoc selection of inference options, the use of guidelines could reduce the controversy focused on individual assessments. Debate will shift to the more general discussion of the generic choice of inference options addressed in the guidelines. Guidelines that are comprehensive and detailed will define and bracket the components of risk assessment most completely and explicitly. Thus, such guidelines could probably provide the sharpest distinction between risk assessment and risk management.

Quality Control

Proponents of guidelines argue that their use would ensure the application of selected inference options based on the informed judgment of experts. A single risk assessment requires knowledge in diverse fields, such as epidemiology, biostatistics, toxicology, biochemistry, chemistry, and clinical medicine. Generally, assessors have advanced expertise in no more than a few fields. Guidelines could help to bridge gaps in knowledge by ensuring that decisions are based on judgments formulated by experts in each subject. Guidelines could also help to ensure that assessors apply judgments that are in accord with current scientific thinking in each field. This argument highlights the importance of including experts from a wide range of scientific disciplines in the formulation of guidelines. Furthermore, it suggests that guidelines should be reviewed periodically so that new scientific developments can be accommodated.

Proponents believe that comprehensive, detailed guidelines would be most helpful in providing guidance to

assessors. Comprehensiveness is necessary to provide guidance on all or most of the components of risk assessment. Detailed guidelines could provide an assessor with an expert's insight into aspects of risk assessment that require special consideration. How flexibility could affect quality control is not clear; however, a flexible framework could have a positive effect, especially if guidelines can help an assessor to know when exceptional or novel scientific evidence should be admitted.

Consistency

Almost all guideline documents have stated, in their introductions, that consistency is a major rationale for guideline use. Consistency in risk assessment is important to the agencies, because it helps to ensure fairness and rationality by precluding the arbitrary application of selected inference options that differ from one time to the next. Consistency also permits comparison of risks associated with different chemicals, and this is useful for priority-setting and for facilitating regulatory decision-making. When the same set of guidelines is applied uniformly by all the agencies, government-wide consistency may be improved. This has important implications for interagency coordination and for reducing the possibility that risk assessments by different agencies will be pitted against each other during litigation on a given chemical. Guidelines of a type that fosters consistency among agencies have yet to be adopted and used. In the absence of such guidelines, there are increased opportunities for inconsistency in the choice of inference options available for each risk assessment component and in the conclusions based on those choices. Proponents of guidelines contend it is often difficult even to know whether there is consistency among risk assessments, because of lack of explicit documentation of inference options used.

Comprehensive, detailed guidelines applied uniformly across the agencies appear to be the most suitable form for reducing inconsistency. To ensure thoroughness and clarity in drawing conclusions, assessors should explicitly document the use of such guidelines in their reports. Flexibility does not imply inconsistency in the application of risk assessment policy. The same inference options can be applied consistently, except in instances where convincing contrary scientific evidence is pre

sented. When such evidence is available, the choice of different inference options has a scientific rationale and does not imply an arbitrary shift in risk assessment policy. It is not the same kind of inconsistency as that which can occur when, for example, one assessor uses a species-to-human conversion factor based on surface-area ratios and another, for no better scientific reason, uses a factor based on body-weight ratios.

Predictability

Proponents of guidelines argue that the private sector should be told explicitly which inference options the government will select to evaluate health-effects data. Industry needs this information to assess its own activities and testing programs. Without uniformly applied guidelines, a regulated party may have to call on the agencies for judgments on numerous issues and have no assurance that the judgments will not change unexpectedly or that one agency's judgment will be consistent with another's. Industry representatives have stated their preference for uniform federal guidelines (although they have been much more cautious in discussing the content of and legal weight given to the guidelines). Consider, for example, the following comment by the American Industrial Health Council, regarding the publication of the IRLG cancer guidelines (AIHC, 1979):

> The report is a significant step toward the formulation of a national cancer policy. AIHC supports the report's stated objective of ensuring that regulatory agencies evaluate carcinogenic risks consistently. We strongly urge that this initial step be followed up so that a national cancer policy is developed and conflicting policies among the regulatory agencies are minimized.

This point of view takes on added significance in view of the increasing desire of some states to develop their own cancer policies. Six states have initiated programs thus far, and California has already published its own guidelines (State of California, 1982a,b). For the private sector to have to contend with a range of different policies in different states would clearly be disadvantageous and burdensome. A federal cancer policy could serve as a model to the states and foster a more uniform approach to risk assessment.

Proponents believe that the most useful guidelines in gauging government actions would be detailed and comprehensive. Although flexibility may undermine predictability, it is reasonable to assume that industry would welcome such a trade-off. Guidelines published as established procedures would be the best option, for the regulatory agencies would not change their procedures without formal notice, but the procedures would not be binding on the regulated parties.

Evolutionary Improvement of the Risk Assessment Process

Proponents of guidelines argue that their use provides a locus for debate, examination, and revision of the selected inference options generally used in risk assessment. By contrast, the argument proceeds, when chemicals are evaluated on an ad hoc basis, the focus of debate is shifted from generic issues to case-specific issues, and the methods and assumptions of risk assessment are obscured from critical view.

Over the last decade, new and refined techniques of risk assessment have emerged. Two important examples are the use of short-term in vitro tests to infer carcinogenicity and mutagenicity and the use of dose-response assessment to estimate the magnitude of human risk at low doses. Guidelines may have contributed to the evolution of both by proposing generic interpretations that would be evaluated and tested both in theory and in the laboratory. The choice of a low-dose extrapolation model is a specific example. The first guidelines (FDA, 1973) proposed the use of the Mantel-Bryan model. This choice was the subject of much debate (FDA, 1977, 1979b); newer guidelines have suggested that this model has been discounted by the agencies, in part because it is essentially empirical and lacks biologic relevance with respect to current knowledge about carcinogenesis (IRLG, 1979b; EPA, 1980a). Furthermore, the debate over an appropriate model helped to foster a major research effort. The ED01 experiment, also known as the "megamouse study," involved the testing of 24,000 female mice given known carcinogens at low doses in an attempt to determine the shape of the response curve at low doses.

Guidelines that are comprehensive and detailed would invite the most opportunity for debate and evolutionary refinement.

Public Understanding

Because risk assessment is complex, it is easy to parody and demean the process. For example, the decision to label soft drinks containing saccharin was satirized in several highly publicized jokes, e.g., "Caution: Saccharin is hazardous to your rat" and "Drink 800 bottles of pop a day and get cancer." Proponents of guidelines argue that comprehensive, detailed guidelines setting forth the scientific and policy bases of risk assessment could improve public understanding and help to dispel the impression that government actions are based on tenuous and inadequate reasoning.

Administrative Efficiency

Some contend that when risk assessments are performed on a chemical-by-chemical basis without the use of guidelines, too many agency resources are devoted to reargument of the same issues with regulated parties. For example: Should animal carcinogenicity data be used to assess human risk? Should data on animals with a high incidence of spontaneous tumors be considered valid? Should benign tumors be assigned the same weight as malignant ones? Which statistical methods should be applied? Guidelines could reduce repetitious discussion by specifying which types of interpretations are acceptable, given the current state of scientific understanding.

OSHA, in its "Identification, Classification, and Regulation of Potential Carcinogens" (1980), registered concern about its efficiency (only seven rule-making proceedings completed in 9 years) and cited one major reason for its low productivity:

> The necessity to resolve basic scientific policy issues anew, in each rulemaking, has increased the burden on the Department of Labor and members of the scientific community called upon to address these widely accepted policies. Moreover, relitigation of these issues in the federal courts has also drained staff time and energy and has inhibited OSHA initiatives while its policy determinations were repeatedly relitigated.

OSHA maintained that the adoption of cancer guidelines was vital to efficient regulation:

> OSHA believes that this general policy and procedure will facilitate the sifting through the evidence concerning substances which may be interpreted to be potential carcinogens. … Without such a system and appropriate criteria, OSHA believes that this task cannot be accomplished in a timely and efficient manner.

Efficiency could best be served by guidelines that are comprehensive, detailed, and inflexible and are adopted as regulations binding on all parties, but this would entail other costs. The disadvantages of such guidelines are described in some of the arguments cited in the following discussion.

Disadvantages of Guideline Use

Oversimplification

The adoption of guidelines may foster a cookbook approach to risk assessment. The more assessors look at chemicals from a generic point of view, the less they are able to draw distinctions among them on the basis of specific data. The critics' ultimate concern is that blind adherence to guidelines might cause scientific information relevant to a particular chemical to be arbitrarily cast aside because it has not been accommodated in the guidelines.

The following underlined phrases are examples of guidelines that critics believe may lead to oversimplification:

- Use of the most sensitive species to determine risk. Critics contend that, if information shows that metabolic similarity to humans is greater for a species that is less sensitive, data on this species may be preferable.
- Absence of a threshold for carcinogenesis. Critics argue that tumors may be induced by a genetic mechanism or by an epigenetic mechanism. In the latter case, a threshold may exist.
- Unqualified acceptance of positive results at

high-dose testing. Critics believe that validity should depend on whether there is a pharmaco kinetic difference between high and low dose. Special consideration should be given to whether detoxifying or repair processes are saturated and to whether competing metabolic pathways are involved and become saturated.

Another potential problem is the lack of attention to weighting of evidence. For example, a guideline may simply state that "positive results in animal tests should always outweigh negative results." This does not take into account the quality and statistical power of the different tests; it could foster the attitude that such considerations are of minor importance.

To a large extent, the strength of such criticisms depends on the form and contents of the guidelines. Those which are comprehensive and leave little latitude for exceptional cases tend to maximize the problem of oversimplification; those which are flexible could be most effective in mitigating the problem. In addition, guidelines may explicitly direct the assessor to consider the weight of evidence of a given test result. For example, the IRLG guideline stated that positive results should supersede negative results, but added a caveat: "If the positive result is itself not fully conclusive or if reasons exist for questioning its validity as evidence of carcinogenicity, the result is generally classified as 'inconclusive' or 'only suggestive' even in the absence of other negative results."

Detailed guidelines can reduce the possibility of oversimplification if the intent of detail is to capture for the assessor the complexity of the issue addressed. For example, a guideline might state the scientific basis for the chosen inference option, the kinds of evidence that are typically applicable, circumstances in which acceptance of exceptional evidence may be appropriate, and other rationales for choosing a particular inference option.

Regardless of the form of a guideline, there are some parts of risk assessment, particularly those dealing with the quality of data and the magnitude of uncertainty, that defy or at least resist generic interpretation. Individual judgment is most important in such cases. A guideline should not be viewed as a formula for producing risk assessments without the need for such judgment.

Mixing of Scientific Knowledge and Risk Assessment Policy

Guidelines unavoidably embody both scientific knowledge and risk assessment policy. In the past, regulatory agencies typically used a conservative approach in the development of risk assessment policy, as in the choice of the most sensitive species, use of the most conservative dose-response curve, and the lack of acceptance of negative epidemiologic data. Industry has been highly critical of this approach. Some representatives believe that risk assessment should be solely a scientific function and should be separated from policy decisions. Consider, for example, the American Industrial Health Council's criticism of the IRLG guidelines (AIHC, 1980):

> When the IRLG report speaks of the importance of using conservative methods or assumptions so as not to underestimate human risk, the report is mixing regulatory considerations into the scientific function. The scientific determination should be made separately from the regulatory determinations. On the basis of the best scientific estimate of the real risk, the regulatory agency can then consider costs, benefits and other elements that enter into a regulatory determination.

Furthermore, there is a fear that the mixing will go unrecognized outside the scientific community (AIHC, 1980):

> When value judgments are formalized by the selection, for "conservative" reasons, of a mathematical model or an assumption used for extrapolating human risk, the fact that value judgments have been made escapes the regulator and the public.

The first criticism appears to miss the crucial fact that risk assessment must always include policy, as well as science. The important issues are what the risk assessment policy content is and whether it will be applied consistently or not. The second criticism is most applicable to guidelines that permit an agency to represent as science the conclusions that have been reached in part on the basis of policy considerations. The argument is less applicable to guidelines that explicitly distinguish between scientific knowledge and risk assessment policy

and direct the assessor to address such distinctions when reaching conclusions. Furthermore, it is not clear that risk assessment performed on an ad hoc basis would reduce the opportunity for unrecognized mixing of science and policy; indeed, carefully designed guidelines could help to inhibit such mixing.

Guidelines very different from the kinds described could be designed to be devoid of risk assessment policy choices. They would state the scientifically plausible inference options for each risk assessment component without attempting to select or even suggest a preferred inference option. However, a risk assessment based on such guidelines (containing all the plausible options for perhaps 40 components) could result in such a wide range of risk estimates that the analysis would not be useful to a regulator or to the public. Furthermore, regulators could reach conclusions based on the ad hoc exercise of risk assessment policy decisions.

Misallocation of Agency Resources to Development and Amendment of Guidelines

Critics contend that the dedication of time and resources to the process of guideline development and amendment detracts from an agency's ability to conduct regulatory activities. For example, OSHA's cancer guidelines required 3 years of effort before promulgation of the final rule in January 1980. The full rule-making record eventually exceeded 250,000 pages. OSHA itself offered some 45 witnesses who addressed the scientific content and the policy implications of the proposal, and a much larger number of witnesses appeared in behalf of other participants. The final policy consisted of more than 280 Federal Register pages of preamble and a dozen pages of regulatory text. Notwithstanding this intensive effort, the guidelines have yet to be applied, and new leadership at OSHA is in the process of reevaluating some provisions of the standard.

The procedures required by the Administrative Procedure Act are so elaborate that development and amendment of guidelines written as regulations are expected to demand more intensive effort than guidelines written as established procedures or recommendations. Regardless of the legal status given to the guidelines, their stability over time is susceptible to major changes in policy stances. However, guidelines that clearly distinguish

scientific knowledge from risk assessment policy judgments could provide a locus for facilitating changes in policy orientation. They would define elements of risk assessment policy that are amenable to change and scientific elements that should not be changed for policy reasons. When risk assessment is done on an ad hoc basis, such distinctions may not exist.

Freezing of Science

Critics believe that guidelines would hinder the timely incorporation of important new scientific evidence during standard-setting. The Dow Chemical Company raised this concern about OSHA's cancer guidelines (OSHA, 1980):

> The record … has now made it clear that there is absolutely no assurance that the latest scientific evidence in the field will be permitted to be applied under the proposal to any given regulation of a specific chemical substance.

OSHA responded to this criticism by incorporating three amendment procedures into its cancer policy: a general review of the guidelines every 3 years by the directors of the National Cancer Institute, the National Institute of Environmental Health Sciences, and the National Institute for Occupational Safety and Health; recommendations at any time from the National Cancer Institute, the National Institute of Environmental Health Sciences, or the National Institute for Occupational Safety and Health; and petitions from the public. Final amendments would occur only through formal, independent rule-making, to ensure that major changes in the guidelines would not be made during the litigation of individual cases. In industry's perception, the amendment provision did not answer its initial criticism. The American Industrial Health Council characterized the amendment procedures as "a time-consuming and ponderous mechanism for incorporating into the regulatory standards newly available evidence or data concerning heretofore unresolved issues" (OSHA, 1980).

This argument is most applicable to guidelines that are adopted as regulations and to those which are comprehensive and inflexible. When guidelines are flexible and adopted as established procedures or recommendations, the rapid incorporation of novel scientific information is

more easily accommodated. The intent of flexibility is to allow the acceptance of exceptional evidence based on convincing scientific justification. In the case of established procedures or recommendations, changes in guidelines could occur without the necessity of a lengthy rule-making process.

CONCLUSIONS

On the basis of its review of the historical record of guideline development and use and its evaluation of the arguments for and against guideline use, the Committee has drawn several conclusions.

1. All agencies have found it necessary to write guidelines, in part, to make their choice of inference options more evident to the public. However, the application of inference options to specific risk assessments has been marked by a general lack of explicitness.

   Because of the lack of explicitness in identifying the choice of inference options in specific risk assessments, it has often been difficult to know whether assessors adhere to guidelines. Within a given program, a consistent set of selected inference options may emerge over time. However, the degree of consistency among programs and agencies is not well defined.
2. Agency guidelines have varied markedly in form and content. Without a deliberate coordinating effort, there is no reason to assume that guidelines will become more nearly uniform.

   Although the scientific bases of cancer guidelines developed in the past by the agencies have been generally consistent, the degree to which the guidelines are comprehensive, detailed, flexible, and legally binding has varied widely. EPA's guidelines are statements of broad principles covering a few components in the four steps of risk assessment; they have no regulatory status. OSHA's guidelines were comprehensive and detailed and dealt mainly with hazard identification; they were regulations. CPSC's guidelines were not comprehensive and dealt mainly with hazard identification; they had no regulatory status. FDA's proposed sensitivity-of-method guidelines are comprehensive and detailed for dose-response assessment and exposure assessment; they are regulations. The formation of the IRLG caused the agencies to adopt a single set of

guidelines for the first time, but, since its disbanding in 1981, there has been no further progress on guideline development.*

3. Uniform guidelines for risk assessment (except for exposure assessment) are feasible and desirable.

Guidelines are feasible. The Committee believes that current statutory requirements would not prevent the use of uniform guidelines. Regulators administer laws reflecting social policies that suggest different degrees of acceptable risk. Some argue that uniform guidelines would keep regulators from applying different standards of risk that were based on these laws. However, regulators can apply such standards on the basis of risk management decisions after completion of the risk assessment. Furthermore, feasibility has already been demonstrated by the adoption of the IRLG guidelines.

Uniform guidelines are desirable for several reasons. First, the use of different guidelines by the agencies could undermine the credibility of their risk assessments. Critics of an agency risk assessment might argue persuasively that another agency estimates risk differently, on the basis of a different set of inference options. Second, almost every regulated chemical is in the jurisdiction of two or more agencies, and the possibility of duplication of effort in performing risk assessments on a given chemical could be minimized if the guidelines were applied uniformly. Adoption of uniform guidelines could foster joint risk assessment efforts by agencies interested in regulating the same chemical; or one agency could rely on the assessment of another agency. Through such cooperative efforts, a small agency like CPSC, which lacks the scientific capability of EPA and FDA, could gain help in evaluating complex data. Third, government-wide guidelines could help industry to gauge government actions and to define the types of data and interpretations relevant to industries' own testing programs. Fourth, federal policy could orchestrate efforts toward uniformity among the states.

* The Office of Science and Technology Policy (OSTP), with agency participation, has written a document describing the scientific basis of risk assessment. OSTP envisions the ultimate evolution of a set of principles for risk assessment from this document.

Exposure guidelines, in contrast with guidelines for other risk assessment steps, are not now readily amenable to uniform application in the various agencies. Apart from EPA, the agencies have rather narrowly defined interests regarding exposure, i.e., foods and drugs at FDA, consumer products at CPSC, and occupational hazards at OSHA. Whereas guidelines for the identification of hazard and for the quantitative estimation of risk in test animals may be commonly applied, no such common basis exists for applying exposure assessment guidelines.

4. Even well-designed guidelines may be unsuccessful unless:

- Attention is given to the process by which they are developed.
- They can accommodate change.
- They are viewed as valuable tools, rather than formulas for producing risk assessments.

Because guidelines must include both scientific knowledge and policy judgments, designing a development procedure is a difficult task. Risk assessment requires advanced knowledge in a number of disciplines, and guidelines should be formulated in part on the basis of the best possible scientific expertness in those disciplines. The best mechanism for determining risk assessment policy must be carefully defined. Because of the necessity of considering policy aspects in guidelines, duly appointed public officials must take responsibility for the policy implications. A major goal of the development process should be the assurance that the guidelines preserve a sharp distinction between scientific knowledge and risk assessment policy.

The Committee believes that guidelines should be capable of accommodating evolving scientific concepts in two ways. First, they should be periodically reviewed and, if necessary, revised. Second, they should permit acceptance of new evidence that differs from what was previously perceived as the general case, when scientifically justifiable. However, an unavoidable trade-off results from the use of such flexible guidelines: predictability and consistency may be reduced for the sake of flexibility.

Every risk assessment involves consideration of case-specific factors, such as the quality of the data or the overall strength of the evidence. These factors cannot

be addressed effectively in guidelines. If assessors were to use guidelines in a strictly mechanical fashion, without recognizing the importance of case-specific judgments, the quality of risk assessments could be diminished.

5. Uniform guidelines for effects other than cancer are desirable, but typically they would be based on a less extensive scientific data base.

   The same reasons enunciated for the desirability of cancer guidelines impel the conclusion that guidelines are needed to guide assessments of other effects. Scientific data available on these effects may be organized to provide useful information for assessing risk. In fact, guidelines have already been developed for some of these (although never adopted by the agencies), i.e., guidelines for mutagenesis (EPA, 1980; March of Dimes Birth Defects Foundation, 1981) and guidelines for reproductive and teratogenic effects (ORNL/EPA, 1982; March of Dimes Birth Defects Foundation, 1981).

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III

Organizational Arrangements for Risk Assessment

The different structures, procedures, and histories of the agencies responsible for regulating toxic substances have produced diversity in their approaches to risk assessment, but common patterns can be discerned, and they permit some broad generalizations about agency organizational arrangements.

First, most agencies have exerted little effort to maintain a sharp organizational separation between employees engaged in assessing the risks associated with substances and those responsible for identifying and evaluating regulatory responses. This is not to suggest that the same persons perform both functions; generally, they do not, for agency organizations reflect considerable specialization, recognizing the distinctive training and capabilities of staff members. However, the two functions are often housed in one organizational unit that is responsible for preparing integrated analyses that incorporate assessments both of risk and of recommended regulatory responses. Sometimes, risk assessment staff are employed in an office that is separate from the office of those who formulate and analyze regulatory options, but, with some notable exceptions, this organizational structure does not lead to a rigid separation of the two staffs.

Second, with the exception of a few experiments in interagency risk assessment during the late 1970s and continuing informal exchanges of information, each agency has performed its own assessments of the risks posed by substances that are candidates for regulation. This operational autonomy does not reflect willful ignorance of the activities of sister agencies or indifference to the desirability of consistency in the evaluation of common candidate substances. Rather, it is a product of

several factors, including the lack of obvious mechanisms for formalized interagency collaboration, the desire of agency policy-makers to reserve authority for policy discretion in reaching conclusions based on risk assessment, the perception that the diversity of types of exposure for which each agency is responsible makes collaborative risk assessment impractical, and differences in regulatory priorities and schedules.

Third, although the four agencies have viewed themselves as ultimately responsible for the risk assessments that support their actions, they often extend their own staff resources available for performing risk assessment by relying on consultants and contractors who are closely supervised by agency personnel. Some agencies—notably the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH)—whose staffs are small or lack needed expertise rely very heavily on nongovernment contractors and outside scientists in the academic community and government research institutions for performance of risk assessments or specific tasks related to risk assessment (such as literature reviews).

In addition, outside scientists are often called on to review assessments produced by agency staff. Such consultations sometimes take place informally, but often through special advisory committees. These committees can be permanent, such as the Environmental Protection Agency (EPA) Clean Air Science Advisory Committee, or can be created to review particular risk assessments, as is done for many of the Food and Drug Administration (FDA) Bureau of Foods assessments. Some are established by statute, with requirements that they review agency assessments before regulations are proposed. Others are created voluntarily by an agency itself. The members of all federal advisory committees are appointed by the agencies, perhaps with the approval of higher executive-branch authority. Candidates for committee membership usually are identified by agency staff, although some agencies seek nominees from professional organizations and other interested parties. Nominations for some statutorily mandated committees are supplied by an external body, such as the National Academy of Sciences or the National Science Foundation. Advisory panels generally exercise considerable influence and, although legally they are only advisory, share to some extent the agencies' authority to reach conclusions about risk.

TABLE III-1 Examples of Four Models of Organizational Arrangements for Risk Assessment

Integration	Intra-agency Separation	Extra-agency Separation	Scientific Review Panels
OSHA Directorate of Health Standards Programs	EPA Carcinogen Assessment Group [a]	NIOSH-OSHA; FDA Drug Evaluation Panels; Committees of the National Research Council	EPA Scientific Advisory Panel; EPA Science Advisory Board Subcommittee on Airborne Carcinogens
FDA Bureau of Foods		National Toxicology Program Panel on Formaldehyde[a]	

[a] Separate, centralized assessment body.

TYPES OF ORGANIZATIONAL ARRANGEMENTS

The prominent proposals for reforms in organizational structures and procedures for risk assessment have featured three interrelated principles:

- Risk assessment activities should be strictly separated from the analysis of risk management options and selection of regulatory strategies.
- Risk assessment activities should be centralized in a single body that serves all regulatory agencies.
- Expert panels composed of nonagency scientists should be used either to perform risk assessments for an agency or to review assessments developed by agency staff.

The Committee outlined four idealized models that reflect various combinations of these three principles. The models are integration, intra-agency separation (with or without centralization), extra-agency separation (with or without centralization), and use of scientific review panels. Examples of agency organizations that roughly approximate each model are identified below and in Table III-I. Most of the examples chosen have many distinctive characteristics that obscure or at least outweigh the three organizational principles. In addition, they are not the only examples of a particular model; others could have been reviewed.*

Integration

In this type of arrangement, a single organizational unit both performs risk assessments and develops regulations. In general, this arrangement is the most common for regulatory programs. For example, for the assessment of chronic hazards involved with chemicals from consumer products, the Consumer Product Safety Commission (CPSC)

* The Committee considered the possible merits of reviewing risk assessment procedures used by other countries as well and decided not to pursue this line of investigation, because of the great differences in political and institutional structures between this country and other countries. Such differences would make it very difficult, if not impossible, to extrapolate findings on institutional structures used in other countries to the United States.

Directorate for Health Sciences is the responsible unit. Before 1977, the Directorate for Health Sciences had few people involved in the risk assessment process, and risk assessments as such were not generally used. Since then, the Directorate has acquired the expertise needed to perform risk assessments itself. The risk assessment is performed within the Directorate, which is distinct from the Commission's politically appointed policy decision-makers. Two different examples of this model examined by the Committee are the OSHA Directorate of Health Standards Programs and the FDA Bureau of Foods (Table III-1). In the former example, risk assessors and those responsible for formulating and recommending regulatory strategies are in the same organizational unit. FDA's Bureau of Foods has a separate office that performs risk assessment, but this separation stems from a functional division of scientific disciplines; it is not intended to and does not result in formal separation of the risk assessment staff from the regulatory staff.

Intra-Agency Separation

In this model, risk assessment is performed by a group that is ostensibly separate from and independent of the office responsible for regulation in the same agency. An intra-agency risk assessment unit could be program-specific or agency-wide. There are examples of program-specific, organizationally separate risk assessment units (notably the Environmental Criteria and Assessment Offices in EPA), but the Committee did not examine them; instead, it reviewed activities of the EPA Carcinogen Assessment Group as an example of an internally separate, agency-wide body.

Extra-Agency Separation

In this model, an agency's risk assessment is developed outside the agency. The examples reviewed demonstrate the wide variety of arrangements included in this model. Full organizational separation can be achieved by having one institution perform risk assessment and a separate institution regulate exposure to hazardous substances. The relation between NIOSH and OSHA was studied as an example of a permanent, statutory arrangement of this kind. A regulatory agency's use of expert panels to

perform risk assessments can also result in extra-agency separation of risk assessment and regulation. Committees of the National Research Council and several groups of panels used by FDA to review the safety and effectiveness of drugs provide varied examples of such arrangements. The National Toxicology Program Panel on Formaldehyde is an example of an ad hoc assessment group that consisted of government scientists, was organizationally separate from the regulatory agencies (although not without agency members), and served all four agencies (i.e., it was centralized). Because the Interagency Regulatory Liaison Group did not perform risk assessments, it has not been examined as an example of an extra-agency assessment body.

Use of Scientific Review Panels

Agencies may use independent scientific panels to perform risk assessments or to review assessments prepared by the agencies. This distinction has been used by the Committee to facilitate separate discussion of panels that perform assessments as examples of full organizational separation (see preceding discussion) and panels that review agency assessments as examples of independent review panels. However, the dichotomy is somewhat artificial, in that there may be difficulty in classifying a particular panel. For example, if a panel responsible for performing risk assessments comes to rely heavily on preliminary analyses prepared by agency staff, it can be thought of as acting in a review capacity. Conversely, panels assembled solely for the purpose of reviewing agency assessments have often displayed remarkable independence, sometimes preparing long critiques of agency documents and suggesting substitute findings and reasons. In such cases, to specify which group had performed and which had reviewed the agency's final assessment of risk is difficult.

The extent to which agencies have used independent scientific panels has varied considerably. For example, OSHA has available two types of advisory committees: standing bodies, such as the National Advisory Committee on Occupational Safety and Health, and ad hoc committees that provide advice on specific standards. Members of both types of committee are expected to be knowledgeable about occupational safety and health and may include persons mainly interested in law or regulatory policies. In addition to their professional expertise, however, members of OSHA committees are intended to be represen

tative of groups interested in occupational health and safety. Several committees have reviewed risk assessments prepared by OSHA or NIOSH. However, because members were intended to be representatives of interest groups, reviews were usually forums for policy debates, not scientific evaluations of risk assessments. In its initial years, OSHA routinely appointed an advisory committee for each regulatory proceeding.

CPSC has had the least experience with expert panels. Before 1981, the Commission was not required to have any assessment of carcinogenic hazard reviewed by an outside panel, although it did make occasional use of such panels (most notably CPSC's request for the National Toxicology Program to form a panel on formaldehyde). CPSC's reauthorization in 1981 included a provision that, before any regulatory action could be proposed on a substance potentially presenting a carcinogenic, teratogenic, or mutagenic hazard, a chronic hazard advisory panel (CHAP) must be established, with the cooperation of the National Academy of Sciences, to review the toxicity of the substance. The first CHAP has recently been convened to review the toxicity of asbestos. Thus, CPSC relies on two methods of peer review for any proposed action. First, independent peer review by outside experts, as well as by a scientific review panel, is performed before a notice of proposed rule-making is issued. Second, the Commission relies on a public rule-making proceeding in accordance with the Administrative Procedure Act during which comment is invited through a Federal Register notice on all aspects of the proposed action. Extensive written comments have been received in the past by this procedure, from industry, consumer groups, members of the academic and scientific communities, and others. Additionally, open, informal public hearings may be held in which interested groups present their views orally; in the past, several such hearings were held during the consideration of a single substance (formaldehyde).

FDA has often used independent scientific panels both to perform and to review agency assessments. The Bureau of Drugs has used standing committees to review and evaluate data on the safety and effectiveness of drug products and to make appropriate recommendations to the Commissioner (see preceding discussion). The use of independent panels by the Bureau of Foods, however, has been on an ad hoc basis, usually at the agency's discretion. However, there are exceptions; for example, the Food, Drug, and Cosmetic Act requires that carcinogenicity

issues related to color additives be referred to a committee of experts selected by the National Academy of Sciences.

EPA, in contrast, has had less choice in its relations with its advisory committees. Several statutes require EPA to consult such committees for scientific review of agency risk assessments or regulations. Examples of mandated advisory committees with a primarily scientific role include the Agency-wide Science Advisory Board; the Clean Air Scientific Advisory Committee, a part of this Board, which reviews criteria documents for air-quality standards; and the Scientific Advisory Panel, which focuses on scientific issues in the Agency's Office of Pesticide Programs. The Committee has examined this panel and a subcommittee of the Science Advisory Board as examples of scientific review panels.

Agency actions, including risk assessments, have been reviewed in the Executive Office of the President; however, because these reviews have, with a few notable exceptions, focused primarily on risk management concerns, the Committee has not examined them.

REVIEW OF AGENCY PROCEDURES FOR RISK ASSESSMENT

This section describes the practices used for risk assessment in each of the organizational examples reviewed by the Committee. The descriptions that follow reveal some strengths and weaknesses of particular approaches and permit some tentative generalizations to be made. Such generalizations, augmented by the experience and judgment of Committee members, lead in turn to recommendations applicable to organizational arrangements for the performance of risk assessment.

The Committee's necessarily retrospective review of agency performance has focused on events and practices of the 1970s, which triggered the current proposals for reform. Changes have been implemented, or at least are contemplated, in the procedures of several of the agencies studied, and the Committee recognized that such changes could alter the performance of risk assessment. Some of the descriptions of agency practices presented here may be dated. However, our purpose is not to describe the current organizational structure of agencies, but rather to discern in the historical record any general relationships between organizational design and procedures and the quality of risk assessments. The

paucity of experience with recent organizational changes and the tendency of any new administration to disclaim the approaches of predecessors while proclaiming the effectiveness of reforms make very recent history less germane to the Committee's purpose.

OSHA's Directorate of Health Standards Programs (DHSP)

OSHA's health standards were expected by Congress to be based on criteria and recommended standards provided by NIOSH. However, improvements in OSHA's scientific capability and a court directive that OSHA itself review all studies included in the risk assessment supporting a proposed standard prompted the agency to rely less heavily on NIOSH and to begin performing its own risk assessments. Until 1976, OSHA had only a few personnel in the health sciences; however, DHSP has since become an organization staffed primarily by health professionals, including industrial hygienists, responsible for performing risk assessments and for preparing standards, relying on economic and technical analyses supplied by the Office of Regulatory Analysis in a separate directorate (Figure III-1). In addition, the Directorate normally has used a number of consultants who assist with risk assessment or other aspects of standard development, contributing considerable specialized expertise to the organization.

OSHA tried to achieve organizational separation of risk assessment from the preparation of standards in the case of carcinogens. One office in DHSP was supposed to do risk assessment, another to draft standards. In practice, however, such separation was not achieved, largely because personnel shortages required that individual staff members perform both functions.

Agenda and Procedures

DHSP's regulatory and risk assessment agenda has been determined largely by two external forces: petitions by labor unions for action on particular hazards and dramatic discoveries of previously unidentified workplace hazards. Court remands of several OSHA standards, such as the benzene standard, provided new work for OSHA, but none of the mandated re-examinations has led to a final standard. Criteria documents prepared by NIOSH also contributed to OSHA's agenda, in that DHSP staff always read these docu

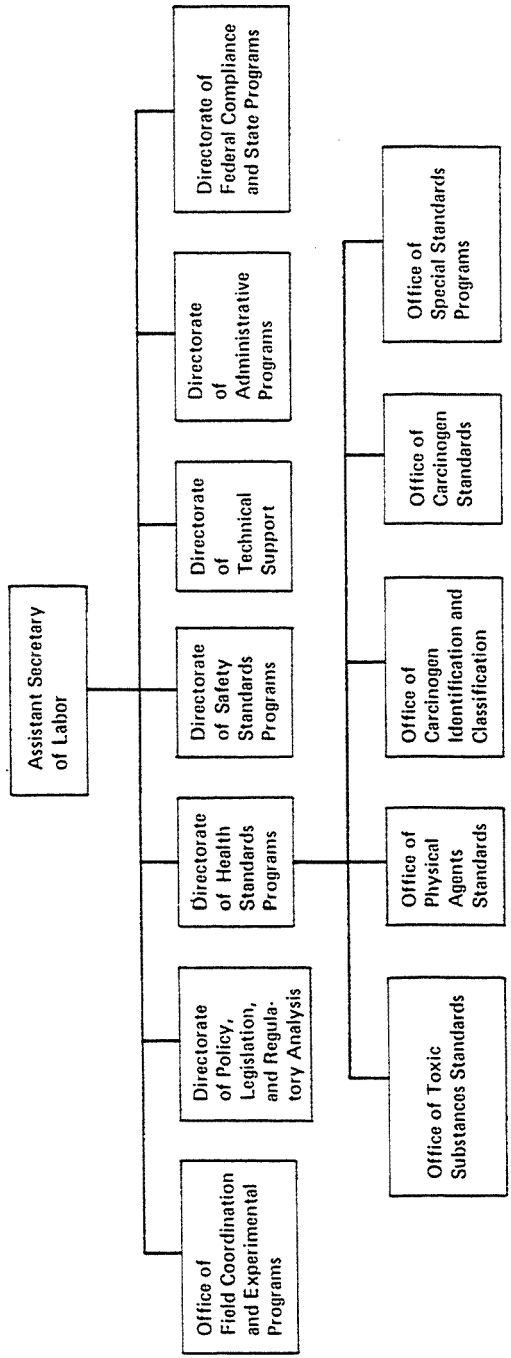

FIGURE III-1 Organization chart of OSHA.

ments when they were received and normally published a Federal Register notice soliciting further information. DHSP's risk assessments usually began with a NIOSH criteria document or other NIOSH input, whatever information was submitted with a labor petition if there was one, the data available from any precipitating discovery, and assessments performed by others, such as the National Academy of Sciences. A literature search and review were conducted by DHSP personnel, often with the help of consultants and NIOSH personnel; and sometimes environmental data on the workplace were solicited or obtained by contractors to contribute to the exposure assessment.

DHSP has not prepared special assessment documents before issuing notices of proposed rule-making. Thus, the first indication provided to the public of the results of an OSHA risk assessment and of the conclusions it intended to draw therefrom was in the Federal Register preamble to its proposed standard. Public comment was invited on all aspects of the proposed standard, including the risk assessment. Extensive written comments were usually received from industry, labor, and others, such as members of the academic scientific community. Customarily a hearing was held at which oral presentations were made and at which questioning of witnesses by OSHA personnel and other witnesses was permitted. The preamble to the final rule, if one were issued, included OSHA's final risk assessment, which incorporated a literature review and OSHA's conclusions on the available scientific data.

In 10 years, OSHA produced permanent health standards for 23 substances or processes, 14 of which were regulated together in a single rule-making. OSHA has also proposed standards for eight substances for which final standards have never been issued, and assessments were conducted for several substances for which new or updated standards are now being considered (Table III-2).

Methods and Use of Guidelines

For most of its history, OSHA has not had formal guidelines for carcinogenic risk assessment. Instead, agency staff have conducted their assessments by choosing options for the components of risk assessment on a case-by-case basis. However, the generic guidelines for identification and classification of carcinogens proposed in 1977 and revised and promulgated in 1980 were intended to

replace criteria used in individual cases with generic guidelines that would be applied consistently to all risk assessments of potential carcinogens. The choices incorporated in the 1980 cancer policy reflected the policy orientations of incumbent senior agency officials. Changes now contemplated in these guidelines reflect the policy orientation of the current OSHA management. Similarly, although for many years OSHA did not perform quantitative risk estimates for use in setting standards for carcinogens, it now intends to do so where appropriate. This change results from policy decisions of senior agency officials, based, at least in part, on their interpretation of the Supreme Court's decision on benzene. (Agency officials have interpreted the decision to mean that quantitative dose-response assessments should be

TABLE III-2 A Summary of OSHA Standards

Standards Completed	Standards Proposed, But Not Completed	Standards Being Developed
Asbestos; Vinyl chloride; Arsenic[a]; Benzene	Arsenic[a]; Beryllium; Sulfur dioxide; Ketones	Ethylene oxide; Asbestos; Ethylene dibromide; Cotton dust, nontextile sectors
Coke-oven emission 14 carcinogens; Lead; Cotton dust; 1,2-Dibromo-3-chloropropane Acrylonitrile	Hearing conservation (noise) Toluene Ammonia MOCA; Trichloroethylene	

[a] The arsenic standard was remanded to OSHA by the Court of Appeals for the Ninth Circuit for purposes of making a significant-risk determination consistent with the Supreme Court's benzene decision.

performed for individual substances if data are sufficient.)

Peer Review

OSHA historically has done a less thorough job than other agencies in obtaining relevant scientific information and independent peer review of this information before issuing a notice of proposed rule-making. Instead, the agency has relied primarily on the public rule-making proceeding to identify new information, much of which is in the possession of interested parties and is unlikely to be brought forward except in the context of rule-making. Similarly, although NIOSH's and OSHA's initial assessments often did not provide a critical review of relevant data, critiques of this information were given to the agency during rule-making proceedings, and the agency's final assessment of the risks posed by a chemical often was substantially changed as a result. OSHA's use of rule-making proceedings to provide scientific review stands in sharp contrast with the other agencies' procedures for review. In the Committee's opinion, this reliance on public proceedings to strengthen and refine the scientific basis for the agency's regulatory actions has not been an adequate substitute for independent peer review. In addition, reliance on public proceedings surely precipitated some of the criticism of agency actions and may have jeopardized the scientific integrity and procedural legitimacy of the agency's risk assessments.

Although OSHA's standard-setting actions have stimulated intense controversy, much of it has focused on issues separate from risk assessment. Questions of costs and technologic feasibility (risk management issues) have stimulated much debate. Discussions of the agency's risk assessments have usually focused on its conclusions and their relationship to the agency's regulatory mandate, rather than on its characterization of risk. When OSHA's risk assessments were challenged during rule-making, some key subjects of contention were OSHA's adherence to the assumption that carcinogens have no threshold for causing adverse effects, its tendency to give positive data greater weight than negative data, its use of single epidemiologic studies to support regulatory action, the validity of specific experiments and the agency's interpretation of the data from them, and the decision as to

whether quantitative assessments of risk should be considered. These issues, of course, have both policy and scientific implications.

FDA's Bureau Of Foods

The Food and Drug Administration enforces the Federal Food, Drug, and Cosmetic Act and several related statutes. Its jurisdiction ranges from basic foods to the most advanced pharmaceuticals and medical equipment. The agency assesses the risks associated with thousands of new and existing products every year, functioning through product-oriented units whose responsibilities are reflected in their titles: Foods, Drugs and Biologics, Veterinary Medicine, and Devices and Radiological Health (Figure III-2). The bureaus' agendas are dictated both through internal planning and by external events, particularly applications for approval of new products. Because the Bureau of Foods has had considerable experience with products that pose potential cancer risks, the Committee has focused on this part of FDA in its review.

Agenda and Procedures

The Bureau's risk assessment functions fall into three broad categories: review of petitions for marketing of new compounds for which the manufacturer provides supporting toxicologic and exposure (or use) data; planned retrospective or cyclic review of approved compounds, supporting data on which the Bureau generally must take as it finds them; and review of inadvertent contaminants in food, supporting data on which are derived from many sources, including open scientific literature, monographs, reports, manufacturers' data, and agency-generated data.

In 1981, the Bureau of Foods evaluated 65 food additives, two color additives, and approximately 45 animal-drug petitions. These totals, however, do not reveal the total number of Bureau inquiries that could qualify as risk assessments, albeit perfunctory. Each time a new contaminant is discovered, for example, the Bureau performs some assessment of the risks, although the available data are often limited and little time is available to gather data before it must decide whether to initiate control measures. Similarly, every reported change in

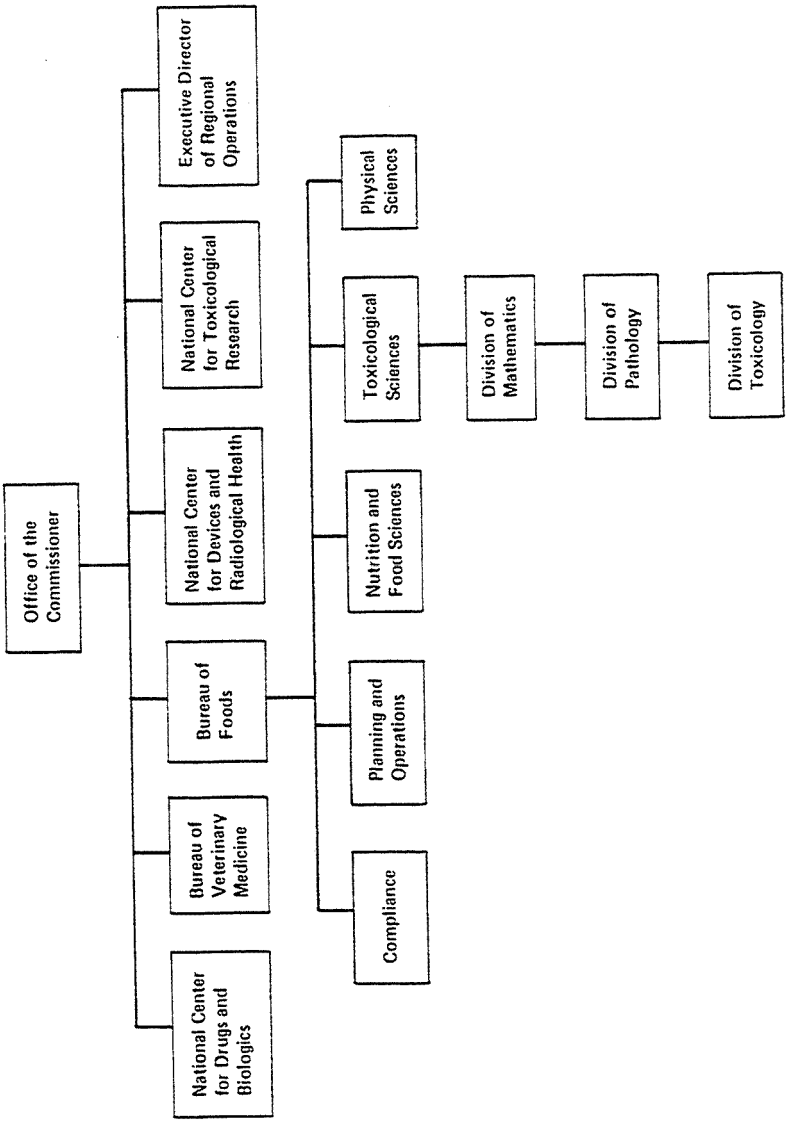

FIGURE III-2 Organization chart of FDA.

degree of contamination invites a new risk assessment. As one would predict, the time and effort required vary with the context. The Bureau's procedures for reviewing food additives, color additives, and residues of animal drugs are more routine than those for evaluating food contaminants, whose occurrence is largely unpredictable. On receipt in the Division of Food and Color Additives, a food-additive petition is evaluated to determine whether it is acceptable for filing. This involves not only review of its formal adequacy, but a preliminary assessment of the toxicologic data to determine whether all potential health effects have been studied.

After official filing of the petition, scientists from the appropriate divisions (ordinarily with the assistance of scientists outside the agency) study the supporting chemical, toxicologic, and exposure data to decide whether the compound is safe. The food-additive law has been construed as requiring, even when the Delaney clause is not applicable, "reasonable certainty" that no consumer will be harmed. No effort is made to evaluate the benefits that an additive might provide, but the Bureau must be satisfied that the additive achieves its intended effects. This exercise usually has two parts: first, Division of Toxicology scientists determine a no-observed-effect concentration for the additive on the basis of acute, subchronic, and chronic feeding studies in animals; second, applying a so-called safety factor, they determine a permissible extent of use in human food or an acceptable daily intake. This value is then compared with the estimated daily human exposure based on the manufacturer's proposed use and predicted human consumption of the foods in which the additive is to be used. An acceptable exposure to an additive is one at which human exposure is at or below the acceptable daily intake. Under current law, this intake value cannot be established for a direct food or color additive that is carcinogenic; such a substance may not be approved for use.

The risk assessment function is performed entirely by Bureau scientists. Bureau staff, including the reviewing scientists, may meet with representatives of the petitioner to discuss uncertainties, request additional data, or suggest reduced use. Typically, both the scientific and the regulatory aspects of food-additive petitions are reviewed and resolved at the division level in the Bureau of Foods. On petitions that raise difficult scientific and policy issues or that pose the question of carcinogenicity, the divisions generally seek advice or direction

from the associate directors, Bureau deputy directors, or the Bureau Director. The Bureau may, in turn, seek advice from the Chief Counsel, from other bureaus, or from the Commissioner's office during the review of petitions that present particular scientific, legal, or policy questions.

Once the responsible unit is satisfied that an additive is approvable and thus that a regulation is appropriate, the Division of Food and Color Additives prepares a document package consisting of an action memorandum, a draft Federal Register document, and supporting material, which is then forwarded through established review channels to the Director's office for final Bureau approval and transmission to the Commissioner's office. The action memorandum recommending approval by the Associate Commissioner for Regulatory Affairs, to whom the Commissioner has delegated formal approval authority, necessarily incorporates both scientific assessments and regulatory judgments. Because the governing legal standard focuses exclusively on the health effects of the additive, the approval process is not influenced by consideration of economic or other benefits.

The sequence of analysis in the Bureau for environmental contaminants does not differ sharply from that described above for food additives, although different divisions may participate in the process and economic factors are consciously considered. The statutory provision under which FDA regulates food contaminants contemplates that it will balance the risk posed by a substance against the effects of reducing consumer exposure, such as loss of food and increases in price. Accordingly, the action memorandum sent to the Bureau Director recommends an exposure limit based on three criteria: an assessment of the risk posed by the contaminant, an evaluation of available method's of chemical analysis to monitor its presence, and an estimate of the economic effects of alternative limits.

Methods and Use of Guidelines

Although the Bureau's approach to the evaluation of acute toxicants has remained stable over a long period, its methods for evaluating potential carcinogens have undergone substantial change since the early 1970s. In 1978, the Bureau Director formed a Cancer Assessment Committee in the Office of Toxicological Sciences to evaluate the carcinogenicity of substances being considered for

approval or regulation and to perform risk assessment. A list of substances reviewed by this Committee in 1981 is given in Table III-3. The 12 members of the Committee are all FDA employees and include toxicologists, pathologists, mathematicians, and chemists. The role of the Committee is to render all final decisions on carcinogenicity for the Bureau of Foods on the basis of scientific information available to it. Its primary function is to determine whether, on the basis of a fair evaluation of all available data, a chemical is a potential or actual carcinogen. Because the Delaney clause, which forbids exposure of any food or color additive that induces cancer, applies to many substances in the Bureau's jurisdiction, quantitative (e.g., dose-response) assessments are not always performed. For some substances, such as contaminants, the magnitude of the risk is relevant, and scientists from the various divisions collaborate with staff responsible for gathering information on human exposure to perform risk characterizations. The Cancer Assessment Committee does not typically prepare formal written assessments, so there is no document available that outlines the relevant data and the rationale for the choices of options made in the assessment of risks. The Cancer Assessment Committee apparently does not follow comprehensive written guidelines, although it does follow some general guidelines that were used in previous decisions and are set out in the agency's drug-residue proposal.

Peer Review

In recent years, the Bureau of Foods has sought independent scientific review of the data on a number of substances. Often Bureau staff informally solicit the judgments of individual outside scientists on major issues. The Bureau routinely uses outside panels established under the auspices of the Federation of American Societies for Experimental Biology for periodic review of substances now generally recognized as safe (GRAS). Ad hoc panels were convened to evaluate the data on such substances as cyclamate, saccharin, Red No. 2, and Red No. 40.

More recently, the Bureau has turned to a standing panel, the Board of Scientific Counselors of the National Toxicology Program. The Board's review of the data on color additive Green No. 5 illustrates the Bureau's approach to external peer review. The Board reviewed the

original data from a study done by a commercial laboratory, which were submitted with a petition for approval of the substance. The Board also considered aspects of the analysis done by Bureau staff and conducted an independent evaluation of the pathology slides and a statistical analysis of the study results. Bureau scientists asked that the Board reach a conclusion concerning the strength of the evidence of carcinogenicity. Thus, the Board was limited to scientific issues and did not consider the possible social implications of its finding. After the Board's finding that the evidence was inconclusive and before the Bureau's conclusion that the additive was unlikely to be a human carcinogen, Bureau staff performed a risk characterization to estimate the potential risks if this conclusion were in error.

TABLE III-3 Substances Evaluated for Carcinogenicity by the FDA Cancer Assessment Committee in 1981

Acrylonitrile	1,2-Dichloroethane
Lead acetate	Diethylhexylphthalate
Vinyl chloride	Diethylhexyladipate
Dioxane	Furazolidone
p-Toluidine	Cinnamyl anthranilate
Hydrazine	Trimethylphosphate

The decision to consult an outside panel for review of risk assessment for potential carcinogens is made by the Chairman of the Cancer Assessment Committee. The Bureau currently is considering establishing a standing committee that could be called on to review agency assessments. It is likely that the impetus to form a standing review committee stems from criticisms of past agency practices, especially those followed in the evaluation of the data on nitrite. In this instance, FDA's contemplated action against nitrite in 1979 was announced before Bureau scientists had had an opportunity to evaluate the critical toxicity data and to refer the data to an independent panel. This controversial chapter in FDA's history of regulating food ingredients has often been cited as demonstrating the need for systematic peer review of the agency's risk analyses in order to avoid the problems that can arise when risk management considerations affect the conduct of risk assessments. The existence of a standing panel, although no guarantee, may discourage

agency officials from deviating from standard Bureau procedures that are now designed to ensure adequate peer review.

EPA's Carcinogen Assessment Group

EPA's Carcinogen Assessment Group (CAG) was created in 1976 by the EPA Administrator to implement generic and uniform agency guidelines for carcinogenic risk assessment. Initially, it was a separate body in the Agency's Office of Research and Development and reported directly to its Assistant Administrator. In 1979, however, the Office of Health and Environmental Assessment was established in the Office of Research and Development, and CAG became one of several assessment groups (Figure III-3). Organizationally, CAG staff are separate from, and independent of, the risk management function; i.e., it is an example of intra-agency separation. It also serves as an example of an internally centralized assessment body, in that it performs assessments for several different regulatory programs in EPA.

Although CAG personnel do meet and talk with regulatory program personnel and are customarily well aware of any programmatic interest in particular substances and of interest-group preferences, this office is insulated from the day-to-day pressures of program offices. Thus, the organizational arrangement that places CAG in the Office of Research and Development does have the initial effect of freeing risk assessment personnel from specific policy issues that arise when risk management options are considered. However, when a scientific review committee examines documents produced by this office later in the process, interest groups are able to express their views and CAG personnel are no longer isolated from such influences.

Currently, all CAG assessments are done by in-house staff, although in the past some were done by consultants. Usually, contractors are employed only for the time-consuming and mechanical task of conducting literature searches. Responsibility for each assessment is assigned to a particular person, but other staff members contribute to various sections according to their particular specialties and expertness. Its staff has been remarkably stable; since 1976, only one person has left the group. As of October 1982, 11 full-time professionals were on its staff, nine of whom had doctorates. Most staff members have an academic background, and their professional work experience averages 10 years. The staff includes

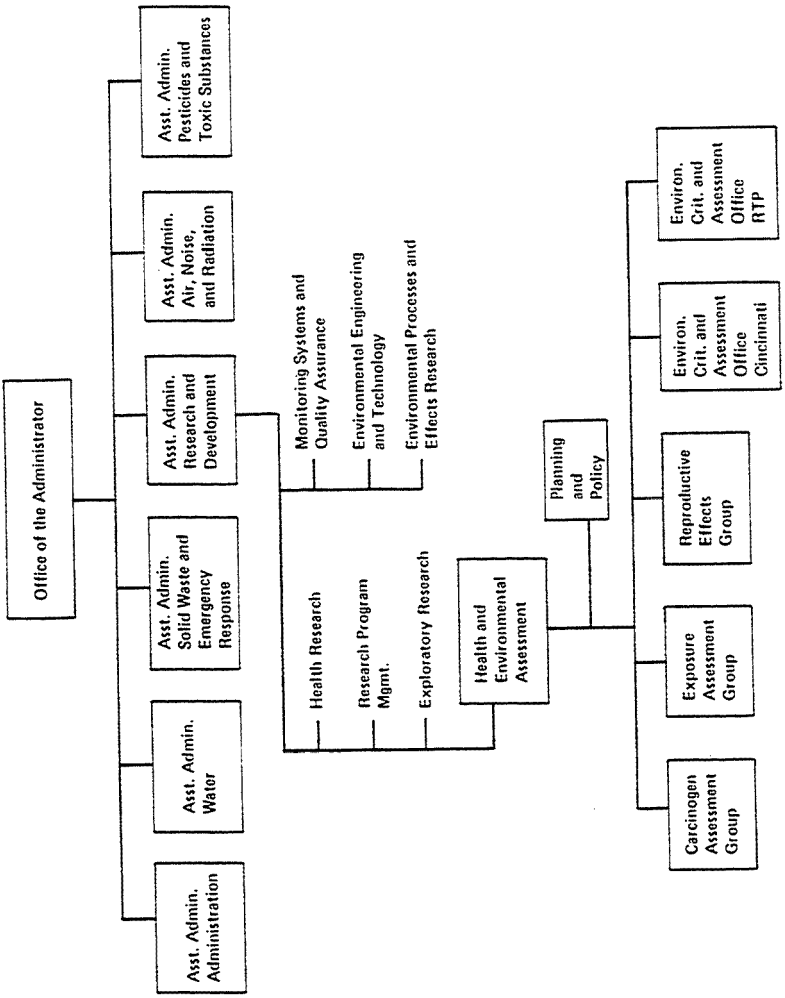

FIGURE III-3 Organization chart of EPA.

three biostatisticians, two biochemists, two epidemiologists, one biophysicist, one pathologist, one pharmacologist, and one endocrinologist. The former Director, now a consultant, is the only physician associated with the office.

Agenda and Procedures

CAG does not initiate its own assessments; instead, it responds to requests from regulatory (program) offices in EPA. It does, however, set its own priorities in consultation with the program offices, on the basis of the workload of requests and the urgency of the need for the assessments. Although it serves as a risk assessment body for the whole Agency, not all programs in EPA use CAG. The most notable exception is the Office of Toxic Substances. Apparently, one factor cited by program offices as leading to this lack of use is the length of time CAG requires to complete an assessment.

Since 1976, CAG has prepared assessments for approximately 150 chemicals. The length and scope of the documents produced vary with the data available, with their purpose, and with the needs of the requesting office. They can range from brief and preliminary literature reviews relevant to hazard identification or tentative estimates of risk as a function of dose to complete and thorough literature reviews leading to a comprehensive risk characterization. In-depth evaluations may or may not include quantitative dose-response assessments. As an example of its work agenda, CAG has covered 41 chemicals for the Agency's Office of Air Quality Planning and Standards. In-depth evaluations were performed for nine (see Table III-4), and preliminary assessments for 32.

Methods and Use of Guidelines

The risk assessments performed by this group are based on Agency guidelines developed initially by CAG in 1976 for use by the entire Agency. These guidelines have been revised after initial publication, and some of the changes have also been published (EPA, 1979, 1980). Normally, individual assessment documents produced do not reexamine or indeed articulate underlying guidelines; rather, the reader is presumed to know that EPA and CAG rely on guidelines that embody particular choices among several

inference options available. Also, the changes made in the guidelines have not, in many cases, been formally acknowledge; i.e., the current guidelines do not exist in a single publicly accessible written document. CAG's use of guidelines, especially for hazard identification, has been regarded by some EPA review panels—notably, the Subcommittee on Airborne Carcinogens—as too inflexible, possibly misleading, and interfering with critical analysis of underlying data. In fact, the initial published guidelines (EPA, 1976) did permit different interpretations of data and the use of different risk assessment methods; however, the methods embodied in CAG assessments and those related to dose-response assessment and published in EPA's Water Quality Methodology for Carcinogens do not reflect this flexibility. The misunderstandings experienced with the Subcommittee on Airborne Carcinogens (and other review bodies) have stemmed to a great degree from the facts that CAG's guidelines are in flux, remain unwritten, and are not presented in the individual assessment documents provided to the review committees. As a result, reviewers are likely to be unaware of the operational ground rules used in interpreting carcinogenicity data and developing risk estimates. The absence of an explicit discussion of the application of Agency guidelines and of discussion of the rationale for the choices made in a risk assessment blurs the distinction between science and policy considerations in CAG assessments.

TABLE III-4 Substances Fully Evaluated by the Carcinogen Assessment Group for the EPA Office of Air Quality Planning and Standards

Arsenic	Methyl chloroform[a]
Benzene	Methylene chloride[a]
Vinyl chloride	Tetrachloroethylene[a]
Acrylonitrile[a]	Trichloroethylene[a]
Coke-oven emission[a]	

[a] Under review as of October 1982.

Peer Review

Drafts are reviewed by all members of the CAG staff and its Director. Drafts are also usually sent for review on an ad hoc basis to knowledgeable persons outside the agency. However, this review process is not part of the public record,and criticism may be accepted or rejected at CAG's discretion. The lack of adequate procedures to ensure that peer review comments are given proper consideration may lessen any benefits to be derived from peer review early in the process of developing a risk assessment. Draft risk assessments are usually reviewed by the Director of the Office of Health and Environmental Assessment, directors of other units in this office, and Office of Research and Development staff before being submitted to the requesting program office. CAG assessments are often submitted to committees of EPA's Science Advisory Board or to the Scientific Advisory Panel for peer review. Such reviews take place in public sessions, in accordance with the requirements of the Federal Advisory Committee Act. They provide an opportunity for interested members of the public to review CAG documents and to communicate criticisms to the reviewing committee and EPA. Reviews of CAG assessments by EPA panels have been mixed, with some panels, such as the Scientific Advisory Panel, often approving the assessments and others finding numerous shortcomings related to both substance and format (e.g., the Subcommittees on Arsenic as a Possible Hazardous Air Pollutant and on Airborne Carcinogens of the Agency's Science Advisory Board). This public review process usually leads to revisions.

NIOSH-OSHA

The Occupational Safety and Health Act of 1970 created two new organizations: OSHA and NIOSH. OSHA was a new component of the Department of Labor. NIOSH was placed in the Department of Health, Education, and Welfare, now the Department of Health and Human Services. Since 1973, NIOSH has been a part of the Centers for Disease Control in the U.S. Public Health Service. The common mission set for both agencies was the protection of the health of American workers. NIOSH's primary functions included the conduct of research and development of criteria for recommendations to OSHA for occupational health standards. In addition, the Act authorized NIOSH to "develop and estab

lish recommended occupational safety and health standards." Although it is not technically correct to refer to NIOSH criteria documents simply as risk assessments, because the documents contain additional information concerning risk management (e.g., engineering considerations) as well as recommended standards, the documents normally included sections that dealt with the adverse health effects of the substances being considered. The health-effects sections would correspond to the Committee's definition of hazard identification.

The legislative history of the Act makes it clear that Congress intended a close coupling between NIOSH's recommendations and OSHA's standards. Nevertheless, relatively few NIOSH criteria documents have led to OSHA standards. This disjunction between the two agencies has stemmed from the difficulty of coordinating two organizations that are physically separated and responsible to different departments. As mentioned earlier, the degree to which OSHA has relied on NIOSH for its scientific expertise has varied. In the early 1970s, OSHA relied heavily on NIOSH for evaluation of health effects; later, OSHA developed its own staff of health scientists and, with considerable help from consultants and contractors, performed its own risk assessments to support agency standard-setting activities.

Because OSHA conducts its own assessments of risk, as well as setting standards, and NIOSH does risk assessments and recommends standards, the relation of NIOSH and OSHA as it has existed since 1976 represents, in some sense, duplication, rather than true extra-agency separation. The earlier relation between the two agencies is, however, an example of extra-agency separation. This section focuses on NIOSH's production of criteria documents during both phases and reflects procedures used throughout the 1970s.

Agenda and Procedures

In the past, NIOSH had an elaborate procedure for setting priorities, which included soliciting nominations of candidate substances from OSHA and the public. In practice, however, before 1976, NIOSH's criteria document agenda was set by agency personnel and the Director, on the basis of their views of the seriousness of various occupational hazards and the number of workers exposed to such hazards. OSHA played little or no role in the selection process,

and NIOSH's agenda for documents therefore did not reflect or greatly influence OSHA's regulatory agenda. One cause of this lack of correlation between the two schedules was their physical and organizational separation. In the late 1970s, NIOSH did receive communications from OSHA that led NIOSH to begin production of process- and industry-oriented criteria documents. Table III-5 lists criteria documents transmitted to OSHA.

Methods and Use of Guidelines

Preparation of a criteria document involved a preliminary review of literature and the identification of gaps in the relevant knowledge. This gap analysis was fed into NIOSH's research planning and led to research directed at filling the gaps. Brief studies could be completed in time for their results to be incorporated into the document. Others would continue after the document was completed and sometimes resulted in revision or updating. The literature review and preparation of a draft document were commonly performed by an external contractor under the supervision of NIOSH personnel. Because NIOSH does not have written guidelines for risk assessment, whether personnel preparing the documents used similar approaches to evaluate data and reach conclusions regarding risks is unclear. NIOSH's failure to develop risk assessment guidelines has helped to obscure the distinction between scientific and policy judgments in the risk assessment process. Although the rationale for separating NIOSH from OSHA has been to allow an independent scientific evaluation without the consideration of economic implications that is necessary in OSHA rule-making activities, the effectiveness of this institutional separation in eliminating the effects of such risk management considerations on the conduct of risk assessment by NIOSH is difficult to determine.

Peer Review

The initial review of a draft criteria document was typically performed by NIOSH staff in the same division of the agency that produced the document. The division draft was then submitted to other NIOSH divisions for review. This was followed by a review performed by knowledgeable experts from industry, labor organizations,

TABLE III-5 NIOSH Criteria Documents Sent to OSHA by May 1982

Substance or Subject	Transmitted to OSHA
Acetylene	1976
Acrylamide	1976
Acrylonitrile	1977
Alkanes	1977
Allyl chloride	1976
Ammonia	1974
Antimony	1978
Arsenic, inorganic	1974, 1975
Asbestos	1972, 1976
Asphalt fumes	1977
Benzene	1974, 1977
Benzoyl peroxide	1977
Benzyl chloride	1978
Beryllium	1972, 1977
Boron trifluoride	1976
Cadmium	1976
Carbaryl	1976
Carbon black	1978
Carbon dioxide	1976
Carbon disulfide	1977
Carbon monoxide	1972
Carbon tetrachloride	1975, 1976
Chlorine	1976
Chloroform	1974, 1976
Chlorophene	1977
Chromic acid	1973
Chromium (VI)	1975
Coal-gasification plants	1978
Coal-liquefaction (Vols. I and II)	1981
Coal-tar products	1977
Cobalt	1981
Coke-oven emission	1973
Confined spaces (as workplaces)	1980
Cotton dust	1974
Cresol	1978
Cyanide, hydrogen, and cyanide salts	1976
Decomposition products of fluorocarbon	1977
Dibromochloropropane	1977
Diisocyanates	1978
Dinitro-o-cresol	1978
Dioxane	1977
Emergency egress from elevated work stations	1975
Epichlorohydrin	1976
Ethylene dibromide	1977
Fibrous glass	1977
Fluorides, inorganic	1975
Formaldehyde	1976
Furfuryl alcohol	1979
Glycidyl ethers	1978
Hot environments	1972
Hydrazines	1978

Substance or Subject	Transmitted to OSHA
Hydrogen fluoride	1976
Hydrogen sulfide	1977
Hydroquinone	1978
Identification system for occupationally hazardous materials	1974
Isopropyl alcohol	1976
Kepones	1976
Ketones	1978
Lead, inorganic	1973, 1977
Logging—from felling to first haul	1976
Malathion	1976
Mercury, inorganic	1973
Methyl alcohol	1976
Methylene chloride	1976
Methyl parathion	1976
Nickel, inorganic and compounds	1977
Nitric acid	1976
Nitriles	1978
Nitrogen oxides	1976
Nitroglycerin—ethylene glycol dinitrate	1978
Noise	1972
Organotin compounds	1976
Parathion	1976
Pesticide manufacturing and formulation	1978
Phenol	1976
Phosgene	1976
Polychlorinated biphenyls	1977
Refined petroleum solvent	1977
Silica, crystalline	1974
Sodium hydroxide	1975
Sulfur dioxide	1974, 1977
Sulfuric acid	1974
1,1,2,2-Tetrachloroethane	1976
Tetrachloroethylene	1976
Thiols: n-alkane mono-, cyclohexane, and benzene	1978
Toluene	1973
Toluene diisocyanate	1973, 1978
o-Toluidine	1978
1,1,1-Trichloroethane	1976
Tungsten and cemented tungsten carbide	1977
Ultraviolet radiation	1972
Vanadium	1977
Vinyl acetate	1978
Vinyl chloride	1974
Vinyl halides	1978
Waste anesthetic gases and vapors	1977
Xylene	1975
Zinc oxide	1975

and universities. In addition, other appropriate government agencies, professional associations, and trade organizations were invited to review the document. After these various reviews were complete and changes were made as deemed appropriate by division staff, the document was forwarded to the Director of NIOSH.

Several shortcomings of NIOSH criteria documents were cited in a recent review of the program funded by the agency: the lack of field experience of criteria document managers, the lack of critical analysis of data, and the alleged disregard of reviewers' comments. The latter claim highlights the importance of procedures that ensure that reviewers' comments are adequately addressed. The lack of critical analysis of data has been attributed at least in part to the facts that the documents were often developed by outside contractors and that NIOSH had little control over the personnel assigned to the contract staff.

Committees of the National Research Council

The National Research Council (NRC) is the operating unit for the National Academy of Sciences' advisory function. As part of this advisory function, NRC has been called on by a number of regulatory agencies to perform risk assessments. Regulatory agencies request assessments by NRC for several reasons, including statutory requirements that particular agencies or programs consult with NRC, inadequacy of agency staff to perform the assessments (as in the case of the FDA request for a review of pre-1962 prescription drugs), and such political objectives as a desire for outside scientific support of an anticipated agency action or a desire to defuse or postpone controversy. Agencies remain free to accept or reject the analyses and conclusions included in NRC reports. NRC risk assessment reports are usually not sufficient by themselves to dictate specific regulatory action, and a separate assessment is usually conducted by the agency, even if in only the most perfunctory fashion.

NRC has done risk assessments for several agencies with jurisdiction over carcinogenic chemicals. However, NRC is in no real sense a centralized risk assessment body and is a very imperfect model for recent proposals to create such a body. First, most of the evaluative work of the NRC is actually performed by individual committees created on an ad hoc basis for each study. Thus, NRC is not a single risk assessment body, but

rather an umbrella for the work of many diverse, if outwardly similar, committees. Second, each ad hoc committee generally reports to a single agency and does not perform assessments for several bodies at once. The committees of NRC have been included in our survey as examples of ad hoc risk assessment groups that are entirely separate from government regulators. Table III-6 is a partial list of NRC reports (published since 1977) that examined the carcinogenic risks associated with exposure to particular chemicals.

Agenda and Procedures

Committee members are appointed on the strength of their professional qualifications; they may come from universities, industry, government, or another sector of society, but they do not serve as representatives of any agency, group, or institution unless they are specifically so designated on appointment. Occasionally when, by virtue of special expertise or for other reasons, persons affiliated with interested parties are placed on committees, every effort is made to achieve a balance of interests. In any case, all committee members are asked to complete a statement, "On Potential Sources of Bias," which includes information on sources of personal income, sources of research support, and more subtle forms of personal bias, including values held that may influence a member's judgment. The membership of every committee that will formulate a position, take an action, or prepare a report is reviewed by NRC staff and must be approved by the Chairman of NRC. The work of the committees is facilitated by professional and support staff employed by NRC.

The conduct of a study varies with its nature and objective, the time permitted to complete it, its political sensitivity, and the personalities involved. In general, committees have considerable latitude in carrying out their responsibilities and may hold public meetings and schedule technical conferences to collect pertinent information. Committees typically meet three to six times a year. Meetings are concerned with planning, discussions of issues and drafts of reports, and, later, the development of final conclusions and recommendations. Although a committee has much freedom in planning and executing its study and reaching its conclusions, several restrictions include the obvious necessity to respond to the charge stipulated in the contract, time and budgetary

TABLE III-6 Some NRC Reports Dealing with Carcinogenic Chemicals (1977-1982)

Report	Parent Unit[a]	Year
An Assessment of Mercury in the Environment	CPSMR	1977
An Evaluation of the Carcinogenicity of Chlordane and Heptachlor	CLS	1977
Drinking Water and Health	CLS	1977
Arsenic	CLS	1977
Nitrates	CPSMR	1978
Saccharin—Technical Assessment of Risks and Benefits	CLS	1978
Polychlorinated Biphenyls	CPSMR	1979
Drinking Water and Health, Vol. III	CLS	1980
The Alkyl Benzenes	CLS	1980
Formaldehyde—An Assessment of Its Health Effects	CLS	1980
Regulating Pesticides	CPSMR	1980
Aromatic Amines: An Assessment of the Biological and Environmental Effects	CLS	1981
Formaldehyde and Other Aldehydes	CLS	1981
The Health Effects of Nitrate, Nitrite, and N-Nitroso Compounds	CLS	1981
Indoor Pollutants	CLS	1981
Selected Aliphatic Amines and Related Compounds: An Assessment of the Biological and Environmental Effects	CLS	1981
Alternatives to the Current Use of Nitrite in Foods	CLS	1982
An Assessment of the Health Risks of Seven Pesticides for Termite Control	CLS	1982
Diet, Nutrition, and Cancer	CLS	1982
Drinking Water and Health, Vol. IV	CLS	1982
Quality Criteria for Water Reuse	CLS	1982
Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents, Vol. 1—Anticholinesterases and Anticholinergics	CLS	1982

[a] CPSMR = Commission on Physical Sciences, Mathematics, and Resources; CLS = Commission on Life Sciences.

limitations, and the necessity for a central NRC-monitored review of the final report.

In addition to providing scientific analyses on which policy or regulatory decisions can be based, NRC reports sometimes make specific recommendations for changes in government policy.

Methods and Use of Guidelines

NRC risk assessments are not easily classified or characterized. Because different committees prepare risk-related reports and NRC does not have any guidelines on the conduct of risk assessments for the committees to follow, approaches and final products show pronounced variations. The absence of guidelines, coupled with the occasional practice of not including a clear explanation of how conclusions concerning risk were reached or of the assumptions used in the quantitation of risk, has led to a blurring of the distinction between scientific and policy judgments made in the assessment of risks. The lack of guidelines has also led to inconsistencies in approach and final decisions among committees. However, the absence of specific guidance for interpreting data and for choosing methods of dose-response assessment or risk characterization is probably to be expected, inasmuch as NRC committees consist of scientific experts whose independent judgments are being sought. Probably only guidelines that are extremely flexible could be adopted by NRC. A subject of much discussion over the last several years has been the value of including quantitative assessments (in our terms, dose-response assessments or, if exposure data are incorporated, risk characterizations) in reports. The trend in recent years has been to include some form of a quantitative risk estimate.

Peer Review

Every report from the NRC is reviewed by a group other than the authors. The process of reviewing is overseen by the Report Review Committee. The reports likely to receive reviews coordinated by that Committee are those judged to have significant policy implications and likely to be controversial; most reports that address risk-related questions would be in this category. (The Report Review Committee also coordinates the review of noncontro

versial reports on an ad hoc basis to monitor the overall quality of NRC reports.) A report not receiving such a review is reviewed under the auspices of its parent commission, independent office, or board. Report Review Committee review entails submission of a draft report to a set of reviewers selected in a cooperative process by the the parent body and the Report Review Committee. These reviewers are invited to comment on technical adequacy and accuracy (the expertness of the authors), on clarity and appropriateness of presentation, on response to charge, on cogency of recommendations with respect to data presented, and on degree of objectivity and freedom from bias. The committee and staff respond to reviewers' criticisms and suggestions, and the responses are examined by a monitor, usually a member of the Report Review Committee, to determine their appropriateness. Thus, a person outside the unit that prepared the report decides whether adequate consideration has been given to reviewers' comments. In cases of persistent and severe disagreement between reviewers and authors, the matter may be referred to the NRC chairman for resolution.

Like the regulatory agencies, NRC has been the subject of controversy in recent years. Some NRC committees have been accused of bias related to their judgments on the risks associated with the substances they are studying. The absence of a member from a discipline that is important for a balanced assessment of risk can also weaken the credibility of an NRC report. For example, an internal NRC study (1981) stated that, in a small sample of risk-related studies completed before 1979, such disciplines as epidemiology were often not represented on the rosters of committees whose subjects appeared to warrant such knowledge.

FDA's Drug Evaluation Panels

Under the Federal Food, Drug, and Cosmetic Act, FDA regulates the marketing of all medicines for human use--prescription pharmaceuticals, over-the-counter drugs, and biologic products, which are also subject to the 1902 Biologics Act. In its efforts to ensure the safety and effectiveness of drugs in these three classes, FDA has relied heavily on advisory panels composed primarily of scientists from academic medicine. Two major programs illustrate the important role of such independent expert panels in agency assessments of human

drugs: the Drug Efficacy Study, a review of the effectiveness of pre-1962 prescription drugs undertaken by NRC in 1966; and the over-the-counter Drug Review, in which advisory panels established directly by FDA have evaluated the effectiveness and safety of ingredients of such drugs.

Both the NRC review and the FDA-directed review enabled FDA to undertake systematic studies of product performance that would have overwhelmed the agency's own resources and personnel. The two reviews differed in a number of respects that may shed some light on optimal structures and procedures for scientific panels.

NRC Review

The 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act required that all new drugs be proved effective, as well as safe, and obliged FDA, after a 2-year grace period, to require proof of efficacy of all pre-1962 drugs. In discharging this obligation for prescription drugs, the agency turned to NRC to establish some 30 panels of six to eight experts in pharmaceutical therapy; each panel was responsible for a class of drugs.

The panels evaluated the data supplied to them by FDA and manufacturers and rated the drugs as effective, probably effective, possibly effective, ineffective, ineffective as a fixed combination, or inferior to other better or safer therapies for the same indications. Their main function was thus to assess therapeutic efficacy, not risk to patient health (except indirectly); all the drugs reviewed had been judged to be safe before original FDA approval. Nevertheless, the panels included comments on the safety of individual drugs, particularly those whose effectiveness was in doubt. An informal NRC coordinating group attempted to review each panel's ratings before forwarding them to FDA, in the hope of ensuring some consistency. In practice, however, the panel's verdicts reached FDA largely unreviewed.

The clinical and other data on which the panels relied came from FDA files, the medical and scientific literature, and the manufacturers of the drugs. The panels neither performed nor ordered any new research, although their assessments often identified subjects on which further studies were needed. The panels met and worked privately; apart from being invited to submit supporting data, manufacturers had no opportunity to participate in the panels' deliberations, nor did representatives of consumers or FDA staff.

To reconstruct precisely how the panels worked or to determine what criteria for evaluation each followed is difficult. The predetermined categories in which they were to rate drugs produced apparent homogeneity in their results, but did not sharply confine or direct their analyses. Evidently, wide variations occurred among the panels. The panels' assessments were reported to FDA largely as statements of conclusions; many of the reports were only one or two paragraphs long. Explanations for the ratings typically took the form of bare references to published studies or invocations of the informed judgment of the panelists. In short, the panels provided verdicts, rather than documented evaluations.

The weight to be given the panels' assessments was not squarely addressed when FDA contracted for NRC assistance. Apparently, it was understood that FDA remained free to accept or reject a panel's judgment, but it must have expected to accept most of the panels' assessments when it contracted with NRC. The agency's primary goal was to spare its own scientific staff the enormous burden of evaluating the effectiveness of thousands of pre-1962 drugs. In practice, FDA has accorded substantial weight to the assessments provided by the NRC panels, usually accepting the rating provided and initiating appropriate regulatory action. A rating of less than "effective" led to notification of a drug manufacturer that more data were needed to support a claim of effectiveness; later (often years later), if data were still considered inadequate, the agency took steps to remove the drug from the market. Some of the agency's efforts provoked protracted litigation and administrative hearings. However, pharmaceutical manufacturers have acceded to the panels' judgments in the majority of instances, occasionally by withdrawing products from the market, more frequently by eliminating claims for which supporting evidence was lacking, and sometimes by sponsoring new clinical research. One important determinant of the acceptance of panel assessments was the commercial importance of the product or claim at issue. When a panel rating and ultimate FDA judgment jeopardized the continued marketing of an important product, the manufacturer often insisted on its full legal rights in the course of combating FDA's efforts at implementation.

FDA-Directed Drug Panels

The NRC review of pre-1962 drugs did not address the marketing status of most over-the-counter drugs. In 1972, FDA launched a second comprehensive review, this time on both the effectiveness and the safety of all active ingredients in over-the-counter drugs. At the outset of this review, FDA chartered 17 advisory committees representing therapeutic groupings. These 17 panels met a total of 522 times over a 9-year period; they reviewed 722 active ingredients for over 1,400 indications and submitted over 75 reports on different therapeutic categories, e.g., internal analgesics, antimicrobials, and vaginal contraceptives.

The central function of these review panels was to report and explain their assessments of the safety and effectiveness of the ingredients used in over-the-counter drugs. These reports were to set forth not only the panels' judgments rating each ingredient (as generally recognized as safe and effective, as unsafe or ineffective, or as requiring additional study), but also supporting documentation and rationale. The panel reports became treatises on the various therapeutic categories, some well over 1,000 pages long. The recommendation segments of the reports were considerably shorter.

FDA intended from the outset to rely heavily on the panels' assessments and thus insisted that they produce thoroughly documented findings. In addition, the panels were required to meet in public and to adhere to other requirements of the Federal Advisory Committee Act. Together, these obligations prolonged the panels' deliberations. Although the Antacid Panel completed its report in less than a year, more complex categories, containing more ingredients, occupied panels for several years, during which they may have met once a month.

The responsibility of producing a fully documented report required the panels to rely on FDA staff to assemble information, handle administrative and stenographic responsibilities, and often do much of the drafting. Thus, the sharp separation that existed between FDA's Bureau of Drugs and the NRC panels never characterized its relation with the over-the-counter panels. However, because discussions of draft reports were held in public meetings and panel members reached their judgments in these meetings, the fact that the final text and judgments represented their views, rather than those of agency staff, was clear. The assessments

of the panels generally have commanded considerable acceptance, because they were reached through public debate and were thoroughly documented.

At the outset of the review, FDA forecast that it would implement most of the panels' assessments. The agency has released the panels' recommendations in the form of notices of proposed rule-making, which are published in the Federal Register as the first step in translating them into regulations. The Bureau of Drugs has expressly reserved the privilege of disagreeing with a panel's findings either immediately or in a tentative final monograph, and it has sometimes done so. These occasions have been few, but usually controversial; and sometimes the Bureau has retreated from its initial disagreement. No manufacturer has been successful in overturning, administratively or in court, a panel judgment in which the Bureau of Drugs concurred.

Perhaps an even better measure of the credence given the panels' assessments is the high degree of voluntary compliance displayed by manufacturers. They have abandoned, albeit often reluctantly, most of the ingredients whose effectiveness the panels have doubted. Almost without exception, they have acceded to the panels' safety judgments. Similarly, they have generally accepted the panels' recommendations for changes in labeling. This remarkable commercial deference to scientific judgment has several explanations, in addition to the credibility of the panels. The slow pace of the review permitted manufacturers to make changes in their formulas or labeling without serious market disruption. The procedures of the panels themselves afforded opportunities for manufacturers to submit information and make arguments before a judgment was rendered. Perhaps as important, the panels' assessments, thus far, have not often jeopardized the continued marketing of major products or whole classes of drugs. If that occurs, it is likely that the panels' findings will encounter more determined opposition.

National Toxicology Program Panel on Formaldehyde

The National Toxicology Program (NTP) was established in 1978 by the Secretary of the Department of Health and Human Services to coordinate all toxicity testing of chemicals in the Department and to facilitate communication between the research and regulatory agencies. NTP

embraces the relevant toxicity testing activities of the National Cancer Institute, National Institute of Environmental Health Sciences, FDA (and its National Center for Toxicological Research), and the Centers for Disease Control. OSHA, EPA, and CPSC also participate in NTP. A major advisory group for NTP is its Executive Committee, which is made up of the heads of the agencies listed above, as well as the Director of the National Institutes of Health and the Assistant Secretary for Health. NTP thus serves as a vehicle for cooperation among the four regulatory agencies—FDA, EPA, OSHA, and CPSC—especially in recommending candidate substances for testing. At least one agency has also called on NTP to review risk assessments: the FDA has on two occasions asked another NTP advisory group—the Board of Scientific Counselors—to review the carcinogenicity data and the agency's analysis of those data on two color additives being considered for agency approval. In addition, NTP has served on one occasion as a structure through which a risk assessment of interest to all four regulatory agencies was performed.

In April 1980, CPSC (in cooperation with the Interagency Regulatory Liaison Group) requested that the NTP help to form an interagency panel on formaldehyde to review the carcinogenicity data on this chemical. The Panel consisted of 16 government scientists, most of whom were experts in toxicology, pharmacology, and epidemiology. Three of the IRLG agencies—EPA, FDA, and OSHA—also supplied scientists as members. Although no employee of CPSC was an official Panel member, a liaison representative of the agency attended all meetings and contributed to portions of the final report. In addition, CPSC personnel assisted the Panel by preparing bibliographies and handling arrangements.

The Panel on Formaldehyde thus serves as an example of a centralized assessment body that, although placed outside the agencies, maintained some association with the scientific staffs of each. The decision to confine the membership to government scientists was driven, in part, by a desire to avoid delays associated with compliance with the Federal Advisory Committee Act's requirements for establishing outside committees. The Panel's creation was viewed as an experiment in interagency coordination.

The Panel met three times. It generally deliberated in private, and its meetings were not announced. The Panel did consult with Chemical Industry Institute of Toxicology scientists who were responsible for designing

and conducting the carcinogenicity study being evaluated, and it permitted both oral and written statements from the Formaldehyde Institute, a trade association of users and manufacturers. Although the Panel reported its findings somewhat later than initially forecast by CPSC, the time required was a relatively brief 6-7 months. One unanticipated delay resulted from the necessity for a second review of the pathology slides from the major study being evaluated. The report stated that evaluation of the findings on carcinogenic effect and other related data convinced the Panel members that formaldehyde is an animal carcinogen when inhaled. This finding has been supported by many other scientists, and the Panel's report has since been published in a peer-reviewed scientific journal. The Panel also concluded that none of the available epidemiologic studies negated the inference that formaldehyde posed a cancer risk for humans. It did not attempt to estimate the risk of cancer for any exposed segment of the population. It did include, however, a quantitative dose-response assessment.

The NTP Panel's formation and performance demonstrate that such ad hoc collaboration is manageable and can function well. Despite the quality of its report and its timely production, however, the NTP Panel's deliberations and report have not yielded any regulatory efficiencies. In early 1982, CPSC banned further use of urea-formaldehyde foam insulation, in part on the basis of the Panel's report, as well as the agency's own risk assessments of formaldehyde's acute and chronic effects. In contrast, EPA has declined to initiate regulation of formaldehyde in response to the Panel's assessment. The Agency declined to act under Section 4(f) of the Toxic Substances Control Act, noting that the animal data available on carcinogenicity did not constitute a "reasonable basis to conclude that [formaldehyde] presents or will present a significant risk of serious or widespread harm to human beings from cancer. …" However, because the Agency's posture is equivocal and not clearly documented, the degree to which it relied on the Panel's assessment in reaching the conclusion is unclear.

Neither of the other two agencies followed CPSC's lead. OSHA declined to issue an emergency standard for worker exposure to formaldehyde, concluding that it poses no imminent hazard; and it recently announced that it was unable to proceed to establish a permanent standard, because the evidence of animal carcinogenicity did not

reveal what, if any, risk exposed workers might confront. These decisions were also based on OSHA's own assessment of risks, but the degree to which OSHA relied on the Panel's assessment for the agency's hazard identification step is unclear. Both EPA and OSHA are continuing to collect data on formaldehyde, but no regulatory action appears likely in the near future. FDA has not acted, because the potential formaldehyde exposures from agency-regulated products were judged to be very low.

The contrasting regulatory outcomes should not be interpreted as indicative that the Panel on Formaldehyde failed in its mission. Although the four agencies planned to consider its report carefully, the Panel's findings were not expected to be binding. Each agency remained free not only to fashion its own regulatory response on formaldehyde, but to qualify, or to dissent from, the Panel's determination of carcinogenicity and estimate of risk. Factors other than the Panel report's validity and utility are more likely explanations for the divergent agency responses. First, the Panel's report was submitted shortly before the 1980 national election, whose outcome forecast fundamental shifts in regulatory policy at EPA and OSHA. Second, the agencies confront exposures to formaldehyde that differ widely in character and intensity, yielding important differences in potential risk. Finally, the statutory criteria governing their decisions could plausibly lead them to accord different weights to the Panel's findings. OSHA, for example, had to decide whether formaldehyde posed a risk sufficient to justify emergency protective measures despite any costs of immediate action.

EPA's Use of Scientific Review Panels

The EPA has had considerable experience with independent scientific panels, but they have served the Agency differently from the risk assessment panels discussed in the preceding section. EPA's panels typically have reviewed the work of Agency scientists and analysts, rather than perform their own risk assessments. Also, most panels serving EPA are mandated by Congress and play legally prescribed roles in the Agency's decision-making process. We examined two such panels: EPA's Scientific Advisory Panel and the Subcommittee on Airborne Carcinogens (a unit of EPA's Science Advisory Board).

EPA's Scientific Advisory Panel (SAP)

The Scientific Advisory Panel was established by Congress in the 1975 Federal Insecticide, Fungicide, and Rodenticide Act to review EPA's evaluations of the environmental and health risks posed by specific pesticide uses. Broadly speaking, the Panel reviews risk assessments prepared by EPA's Office of Pesticide Programs to support contemplated regulatory actions against hazardous pesticides. It also reviews the proposed and final forms of such actions. Consultation was initially required only when the Agency contemplated suspending or canceling a pesticide's registration or issuing general regulations governing pesticide registration. Cancellations and general pesticide regulations must be submitted to the Panel for review before they take effect. Suspensions of registration do not require prior review, but EPA must submit the underlying studies for review promptly after any suspension action. EPA must also submit for peer review the "design, protocols, and conduct of major scientific studies" conducted under the pesticide act. The following description reflects activities undertaken before September 1981.*

The Panel normally consists of seven members selected by the EPA Administrator from among six persons nominated by the National Institutes of Health and six nominated by the National Science Foundation. Until its last meeting in June 1981, the Panel generally met once a month. Topics covered during 1980 and 1981 are shown in Table III-7. The Panel does not set its own agenda, although the chairman may control the sequence and conduct of individual sessions. The risk assessments that the Panel reviews are selected by the two divisions (Hazard Evaluation and Special Pesticide Review) of the Office of Pesticide Programs that use its recommendations. Virtually all the scientific and exposure information available to the Panel is provided by the division whose assessment is being reviewed, although much of this information comes originally from the registrant of the product in question. Panel members necessarily accept the authenticity of the information provided, although they sometimes question its quality.

* Authorizing legislation expired in September 1981, and new legislation has not been enacted (as of December 1982).

TABLE III-7 EPA Actions Reviewed by the Scientific Advisory Panel (1980-1981)

A. Regulations under Section 25(a) of The Federal Insecticide, Fungicide, and Rodenticide Act
   1. Final Rulemaking for Registering Pesticides in the United States, Subpart E, Hazard Evaluation: Wildlife and Aquatic Organisms
   2. Proposed Rulemaking for Registering Pesticides in the United States, Subpart L, Hazard Evaluation: Nontarget Insects
   3. Proposed and Final Rulemaking for Registering Pesticides in the United States, Subpart D, Chemistry Requirements: Product Chemistry
   4. Final Rulemaking for Amendment of 40 CFR 162.31 by Adding Certain Uses of Eight Active Ingredients as Restricted Pesticides
   5. Proposed Rulemaking for Registering Pesticides in the United States, Subpart M, Data Requirements for Biorational Pesticides
   6. Final Rulemaking for Registering Pesticides in the United States, Subpart N, Chemistry Requirements: Environmental Fate
   7. Informal Review of Draft Proposed Pesticide Registration Guidelines, Subpart K, Exposure Data Requirements: Reentry Protection
   8. Review of Proposed Pesticide Registration Guidelines, Subpart H, Labeling of Pesticide Products
   9. Review of Final Rule on Classification of 11 Active Ingredients for Restricted Use

B. Cancellations under Section 6(b) of the Federal Insecticide, Fungicide, and Rodenticide Act
   1. Dimethoate
   2. Diallate
   3. Lindane
   4. Strychnine
   5. Ethylene dibromide
   6. Oxyfluorfen (Goal 2E)
   7. Wood preservatives, pentachlorophenol, creosote, arsenicals

Meetings are open to the public, and interested parties are generally encouraged to make presentations. These meetings sometimes focus on risk management issues, rather than on the health and environmental assessments submitted to the Panel, in part because participants making presentations are not confined to addressing scientific aspects of the Agency's risk assessments. Equally important in the consideration of nonscientific issues has been Congress's decision not to restrict the Panel to a strictly scientific review of the Agency's risk assessments. (The Panel's mandated review responsibilities extend to contemplated EPA actions that combine both risk assessment and regulatory policy elements.) Although the rationale for the Panel's creation was to introduce independent scientific review into EPA's deliberations, the mechanism chosen has routinely resulted in the Panel's commenting on the Agency's choice of regulatory options. The Agency has sought to anticipate the Panel's tendency to stray from the scientific issues before it and has attempted to frame specific questions on which comments are requested.

The participation of the Panel probably has improved the quality of EPA analyses and added to their credibility among both environmental and industry groups. However, expectations of some EPA critics that it would repudiate the Agency's scientific analyses have not been realized. Over the last 5 years, the Panel has agreed with most Agency risk assessments brought before it. There have been some notable exceptions, such as the Panel's disagreement with the Agency's handling of 2,4,5-T. The endorsement of most Agency assessments and Agency actions based on those assessments by the Panel have been extremely helpful in improving Agency credibility and rendered its actions less vulnerable to challenge in administrative or judicial hearings, as with the Panel's support of EPA action on wood preservatives. The Panel's success can be traced to several causes: its public deliberations, which may have made it difficult for EPA to ignore its comments; its continuity (until its authorizing legislation expired), which permitted it to understand EPA's approaches and simultaneously strengthened its influence with EPA staff; and the scientific distinction of individual Panel members.

In the case of EPA's decision to suspend use of 2,4,5-T and Silvex (its companion product) for some applications and to hold wide-ranging hearings on other applications, the Panel declined, after 3 days of public meetings, to support the Agency's proposed proceedings.

The Panel believed that additional data, including results of further tests for carcinogenicity and reproductive toxicity and of more complete monitoring for residues, were required before a hearing could be held profitably. Because EPA had not asked the Panel to approve the holding of a hearing and believed that it would be more efficient to deal with all uses of 2,4,5-T at one time, the Agency persisted and announced a hearing on the risks and benefits of 2,4,5-T, which began in March 1980. This difference, coupled with congressional displeasure with EPA's original suspension of 2,4,5-T and Silvex, led ultimately to the 1980 statutory amendment mandating that the Scientific Advisory Panel review the studies that underlie suspension decisions.

EPA's Subcommittee on Airborne Carcinogens

The Subcommittee on Airborne Carcinogens, a part of EPA's Science Advisory Board, was not mandated by statute. It was created in 1980 at the request of the Assistant Administrator for Air, Noise, and Radiation to review the assessments that the Agency is statutorily required to submit for Board review. Members of this Subcommittee were appointed by the Administrator; however, it no longer exists, having recently been merged with the Environmental Health Committee of the Science Advisory Board.

The Subcommittee reviewed six pairs of draft documents that included hazard identification and dose-response assessments produced by the Carcinogen Assessment Group and exposure assessments produced by private contractors for EPA's Office of Air Quality Planning and Standards. The chemicals evaluated in those documents were trichloroethylene, perchloroethylene, methylene chloride, methyl chloroform, acrylonitrile, and toluene. Subcommittee members reviewing these documents included a biochemist, a biostatistician, a pathologist, an engineer, an oncologist, a toxicologist, and a meteorologist. Five members were affiliated with universities and one with a research consulting organization; the seventh was a private consultant.

In accordance with the Federal Advisory Committee Act, the Subcommittee's review was held in public and announced in the Federal Register, and interested members of the public were invited to make oral and written presentations. Several such presentations were made, primarily by representatives of industries that would be affected

by EPA regulation of the substances under discussion. EPA and contractor personnel also attended the review and participated actively, briefing the Subcommittee on the contents of documents, answering members' questions, and defending their work against criticism.

The Subcommittee did not write a report after its review, and the absence of a summary report has led to some confusion regarding the nature of its criticisms. Review of the transcript of its second meeting (September 5, 1980) and discussions with various participants in that review meeting have revealed several general criticisms of the Carcinogen Assessment Group's risk assessments. One was that the documents provided to the Subcommittee were not sufficiently detailed; i.e., they did not provide enough scientific information from the various studies cited to permit the Subcommittee to make an independent assessment of the quality and validity of the studies. Another criticism raised by the Subcommittee was that the conclusions drawn did not reflect the quality of the data on which the risk assessments were based. Some Subcommittee members asserted that such considerations may, in fact, be precluded by rigid adherence to the Agency's guidelines for risk assessment.

Other criticisms focused on specific issues, including the validity of basing a conclusion of carcinogenicity on an increase in mouse liver tumors, the importance of contaminants in the test chemicals, and the wisdom of using a single model for extrapolating from high to low doses. The Subcommittee viewed these issues as primarily scientific, whereas Agency staff considered them, although resting on scientific principles, as resolvable through the choice of conservative policy options—a choice embodied in the Agency's guidelines. These differences between the Subcommittee and Agency staff emphasize the conclusion set forth in Chapter I that many components of risk assessment lack a firm scientific answer and require a judgment to be made. In some cases, such judgments may be informed by scientific arguments, but may ultimately rest on policy preferences. The difficulties in communication between the Agency and the Subcommittee also underscore the importance of explicit risk assessments and written reviews.

The differences reported above have not yet been fully resolved. The Agency's experience with the Subcommittee highlights some difficulties in using a review body that has not had sufficient time to develop a working approach to its task. It also emphasizes the importance of ex

plaining Agency risk assessment procedures, including the adherence to specific guidelines, to review panels. Concerns similar to those of the Subcommittee have been expressed by members of the Environmental Health Committee, which replaced it, and Agency staff are currently considering changes in the risk assessment procedures embodied in their guidelines.

PROPOSED CHANGES IN ORGANIZATIONAL ARRANGEMENTS FOR RISK ASSESSMENT

Proposals to reform the organizational arrangements for risk assessment have been advanced to reduce perceived shortcomings in agency practices. The criticisms to which these proposals respond may be summarized as follows:

- Bias. Critics of agency performance suggest that decision-makers approach risk assessment with attitudes about regulation that preclude objectivity. Regulators, for example, may skew their assessment of risks associated with a particular substance to support a preference to regulate or not to regulate that substance.
- Exaggeration. This criticism is closely related to the first. The suggestion is that regulatory agencies, accustomed to operating in an adversary mode and expecting their judgments to be challenged in administrative hearings or in court, typically overstate the risks associated with hazards that they decide to regulate or understate the risks associated with hazards that they decide not to regulate. The instinct to support a position with every available argument may distort interpretations of scientific data, choice of extrapolation procedures, and assumptions about human exposure. The critical role of legal staff in preparing agency documents is thought to foster the adversarial style.
- Poor Public Understanding. If risks are misdescribed, it follows that public perception of the risks will be inaccurate. In addition, because agency announcements of regulatory actions typically stress the ultimate risk management strategy, such as the banning of saccharin, and do not explain why a particular action is being taken, the public is led to infer the degree of risk from the action proposed or from the decision not to act. However, an agency's ultimate decision may be dictated by statutory language or regulatory policies that emphasize considerations other than degree of risk.

- Poor-Quality Personnel. This argument is straightforward, if unflattering. It is that regulatory agencies cannot attract or retain adequate numbers of highly qualified scientists to perform risk assessments. Many of their personnel are removed from active research by time and distance and are unfamiliar with the latest developments in their fields.
- Inconsistency. This criticism supports proposals for centralization of risk assessment. To the extent that separation is a prerequisite to centralization, this criticism would also support institutional separation. The suggestion is simply that agencies have applied inconsistent criteria and reached inconsistent results in assessing the risks posed by the same hazards. Such inconsistency is more likely when each agency is responsible for performing its own assessment.
- Redundancy. Starting from the assumption that different regulatory agencies have been, and are likely often to be, concerned with the same hazards, the critics argue that current arrangements force government regulators, affected industries, and interested scientists to deal with litigation on the risks of a given substance several times. Accordingly, a central institution responsible for performing risk assessments for all agencies might yield process efficiencies and reduce costs for all participants.

Description of Proposals

The central proposals for changes in institutional arrangements for risk assessments developed by the office of Science and Technology Policy (OSTP) and the American Industrial Health Council (AIHC) and presented in H.R. 638 have sparked much of the current debate and precipitated this study. For several years before, however, dissatisfaction had been expressed with the procedures by which government bodies used scientific data and resolved what purported to be scientific issues. This dissatisfaction led to one of the precursors of the current proposals: the idea of a science court for resolving scientific issues underlying regulatory decisions. That suggestion and other, more recent proposals for procedural and structural reforms are discussed briefly below. The primary objective of this section, however, is to facilitate evaluation of the three main proposals that inspired this study.

Science Court

An important precursor of the OSTP proposal was the science court concept of Kantrowitz (1975). The science court was proposed to assist decision-makers with disputed scientific aspects of a decision. Hence, a basic premise of the science court is that it is both possible and desirable to separate the scientific elements of a public-policy decision from social and political considerations. The judges of a court were to be impartial, competent scientists from relevant disciplines who were not involved in the dispute. These judges would hear testimony from scientific experts on both sides of the issue, who would be allowed to cross-examine each other. The rationale was that scientist advocates are best qualified to present their own cases and to probe the weaknesses of their opposition. In the environment created in such a court, complete objectivity would be neither assumed nor necessary. After hearing all witnesses, the judges would issue a summary of their opinion of the meaning of the scientific evidence. Their opinions would deal only with scientific questions and could not include recommendations for public policy. Many details of a science court's procedures and operations are, however, unclear. Even after several years of sometimes heated debate in the scientific and regulatory communities, the overall reactions to the concept can be characterized as at best only lukewarm. Although a genuine science court will probably not be established, the underlying idea of separation of scientific issues from social and political considerations in decision-making has since appeared in other proposals.

FDA's creation and use of public boards of inquiry is the nearest analogue to the science court that has been put into practice. In 1975, FDA, on its own initiative, adopted regulations describing a public board of inquiry, a new kind of decisional body that could substitute for the traditional trial type of hearing before an administrative law judge if parties to formal disputes before the agency could agree. A board of inquiry is an ad hoc panel of three independent scientists, qualified in relevant disciplines, who hear evidence and arguments and render a preliminary decision, which may be appealed (like that of an administrative law judge) to the Commissioner of FDA. The procedure assumes that disputes that are primarily scientific can be resolved more accurately, faster, and with greater credibility by an

expert tribunal. FDA's novel procedure has been tried only once, to resolve safety issues concerning aspartame, a new artificial sweetener. This experience yielded, at best, equivocal support for the new procedure. Perhaps because of its novelty, the process took over a year to complete. The parties disagreed at length over the makeup of the board, the objectivity of its members, and the procedures it should follow. The FDA Commissioner ultimately rejected the board's conclusion that aspartame should not be approved and issued an opinion that both questioned the board's scientific rationale and corrected its interpretation of the legal criteria for approval of food additives. Other regulatory disputes, including FDA's refusal to approve the injectable contraceptive, Depo-Provera, are scheduled to be heard by boards of inquiry.

OSTP Proposal

A 1978 report from OSTP gave impetus to emerging proposals for separation and centralization of scientific aspects of risk assessment. The report recommended several steps to ensure consistency in the identification, characterization, and assessment of potential human carcinogens. Two interrelated stages in regulatory decision-making were delineated: Stage I, identification of a substance as a potential human carcinogen, qualitative and quantitative characterization of the risk it poses, and explication of the uncertainties; and Stage II, evaluation of regulatory options and their consequences. This dichotomy closely parallels our own distinction between risk assessment and risk management. The OSTP report recommended that a uniform decision-making framework be used in all agencies and that Stage I and Stage II functions be separated within or outside regulatory agencies while sufficient linkages were maintained to ensure relevance and timeliness. Such organizational experiments as the Carcinogen Assessment Group in EPA were highlighted. The report also suggested that the then-fledgling National Toxicology Program might eventually assume an expanded role in coordinating or overseeing some risk assessments for the regulatory agencies.

H.R. 638 and the AIHC Proposal

The 1978 OSTP report was a broad statement of principles. Two detailed proposals to create new risk assessment institutions have since been advanced. Because these proposals have several features in common, but also present important contrasts, they are summarized together (Table III-8).

In February 1980, Representative William Wampler first introduced legislation (U.S. Congress, 1981c) to establish a National Science Council. H.R. 638 calls for the creation of a new panel of scientists, entirely independent of the regulatory agencies, that would decide disputed scientific issues posed by regulatory initiatives. The AIHC had previously (1979) advanced a similar proposal to create an expert science panel that would evaluate the hazards of chemicals considered for regulation. Both proposals stress the importance of uniform, consistent resolution of the scientific questions underlying regulatory decisions. Both espouse the separation of risk assessment from the design and selection of regulatory responses, and both would use independent scientific experts to perform the assessments.

There are some basic differences between the two proposals. Under H.R. 638, any party could request referral of scientific issues to the National Science Council. The AIHC proposal specifies that, although any party may request a review, only federal agencies or Congress would have the authority to initiate mandatory review of scientific questions by the central science panel. H.R. 638 would apply only in formal adjudications. The AIHC proposal would apply to any agency proceeding in which risk assessment was at issue. Because rule-making is the primary mode for regulating hazardous substances, the AIHC proposal would apply to more regulatory actions than would H.R. 638. Under H.R. 638, decisions of the National Science Council would be binding on regulatory agencies. In contrast, assessments of the AIHC's science panel would not bind the agencies, but would carry a presumption of validity, subject to rebuttal in later regulatory proceedings.

The risk assessment bodies contemplated by the two proposals also differ in composition and procedures. The National Science Council would be a standing body of 15 full-time voting members serving 2-year terms. Individual chemicals would be assessed initially by advisory panels made up only of Council members. Each panel would have

TABLE III-8 Comparison of Major Features of H.R. 638 and the AIHC Proposal

H.R. 638	AIHC Proposal
Structure: Single continuing panel separate from agencies; centralized	Single continuing body with rotating members; in the NAS[a]
Membership: 15 full-time members appointed by chairman of NSB[b] from NAS nominees; members to be qualified, distinguished scientists	15 part-time members selected according to NAS procedures; members to represent the best scientists
Scope: Referral by any party of adjudications involving harm to human health from substances considered by CPSC, FDA, USDA,[c] DHHS,[d] OSHA, and EPA	Referral by any party or agency (only latter require mandatory consideration) concerning proposed rules or agency adjudications; all agencies with regulatory jurisdiction would be affected
Functions: Panel could prepare an independent risk assessment; its decision would be binding on the agency	Panel could prepare an independent risk assessment; its findings would be advisory, but would be part of record
Public Participation: Parties to adjudication would be involved	Federal Register notice of referral would solicit submission of data by public
Implementation: Legislation	Legislation

[a] National Academy of Sciences.
[b] National Science Board.
[c] U.S. Department of Agriculture.
[d] Department of Health and Human Services.

at least five voting members. The AIHC science panel would be established under the umbrella of the National Academy of Sciences and consist of 15 part-time members who would serve for terms of 3 years. The panel could establish working groups, which could be composed largely of outside experts. These divergent approaches to placement and composition of the panels and terms of members reflect different expectations about which status would attract the best scientists and perhaps about the extent to which the results would be binding. For example, the AIHC proposal assumes that distinguished academic and industry scientists would be unwilling to serve on a full-time basis for any substantial period.

Under H.R. 638, the National Science Council would decide scientific questions after conducting a formal "hearing on the record," in which all parties to the agency proceeding could participate. Under the AIHC proposal, referral of scientific issues to the panel would be announced, and the submission of written evidence and arguments would be invited. The less formal procedures visualized by the AIHC are consistent with its objective of obtaining nonbinding expert judgments on scientific issues that underlie decisions.

The two proposals embody different expectations as to speed of response. H.R. 638 would require the National Science Council to make a final report to the referring agency within 90 days of receiving a dispute. The AIHC proposal, however, imposes no time limits on the panel's assessment, except that the panel "operate expeditiously but not precipitously" (Higginson, 1982).

Single-Agency Proposals

H.R. 638 and the AIHC proposal espouse government-wide reform of the institutional means for risk assessment. Other notable recommendations for institutional restructuring have been addressed to individual agencies or agency programs. In 1981, for example, Senator Orrin Hatch introduced legislation (U.S. Congress, 1981d) to amend the food-safety provisions of the Federal Food, Drug, and Cosmetic Act. His bill included a provision permitting FDA to request, or affected third parties to demand, assessment of the risks associated with specific food constituents, with such assessment to be performed by a panel of scientific experts appointed by the National Academy of Sciences. The panel's assessment would be

advisory, rather than binding on the agency. Similar provisions have appeared in other proposals to revise government regulation of food safety, including a proposal developed by the Food Safety Council (1979). These proposals appear to share assumptions underlying the AIHC proposals: that agency risk assessments cannot be assumed to be objective, thorough, or expert and that an independent review should be available before a final decision is made. These proposals for independent scientific panels differ from H.R. 638 in three important ways: they would apply to one agency or program; they contemplate only an advisory role, rather than a resolving function, for the scientific panel; and they would apply to any agency proceeding in which risk assessments were at issue. The proposals thus can be viewed as agency- or program-specific illustrations of the AIHC proposal to create one central scientific panel to serve all agencies.

One such single-agency proposal has been adopted. In 1981, Congress amended the Consumer Product Safety Act (U.S. Congress, Omnibus Budget Reconciliation Act, 1981a) to require CPSC to consult with an ad hoc chronic hazards advisory panel whenever it contemplates rule-making concerning a product believed to pose a risk of cancer, birth defects, or gene mutation. A panel will consist of seven members appointed by the Commission from among 21 scientists nominated by the President of the National Academy of Sciences. Nominees may not be employees of the government or have any financial ties to any manufacturer or seller of consumer products. Each nominee must have "demonstrated the ability to critically assess chronic hazards and risk to human health presented by the exposure of humans to toxic substances or as demonstrated by the exposure of animals to such substances." The panel's responsibility is to prepare for the Commission a report on the substance that the agency is considering regulating. The panel is to review the scientific data and other information related to the substance and "determine if any substance in the product is a carcinogen, mutagen, or teratogen." The panel will also "include in its report an estimate, if such an estimate is feasible, of the probable harm to human health that will result from exposure to the substance." The Act requires that a panel submit its report within 120 days of convening, unless the Commission allows it additional time. A panel's report "shall contain a complete statement of the basis for its determination." The Commission must consider the panel's report and incorporate its evaluation into any advance

notice of proposed rule-making and any final rule. Apparently, the agency is not bound by a panel's determination of carcinogenicity or its estimation of the risk associated with exposure. Although it appears that each panel is to perform its own risk assessment, the statute is silent on the role to be played by agency staff and on the weight that a panel might legitimately accord to analyses prepared by the agency itself. These panels are exempted from the Federal Advisory Committee Act; the exemption presumably means that they are not required to provide advance notice of their meetings or to deliberate in public. A panel may seek information from third parties, but only through CPSC.

Criticisms of Proposals for Separation and Centralization

The four federal regulatory agencies have responded skeptically to proposals to separate and centralize the function of assessing the risks of chemicals that are candidates for regulation (U.S. Congress, 1981b). Other observers have also found flaws in the proposals. A central criticism made by those who argue against full organizational separation between risk assessment and regulatory policy-making is that simply separating risk assessment from the regulatory agencies would not separate science from policy. This argument is based on the fact that the risk assessment process requires analytic choices to be made that rest, at least in part, on the policy consideration of whether to be more or less conservative when determining possible public-health risks. A second point is that, although extra-agency separation of risk assessment may help to minimize the influence of risk management considerations on this process, the agency responsible for deciding what exposure to permit or what costs to impose must make what is ultimately a political judgment based on the extent of risk determined in the risk assessment and often on the benefits and costs of regulatory action and its feasibility and political acceptability. For its decision to be politically acceptable and the decision-maker accountable, the agency must have responsibility for each of these components of regulatory decision-making. A third argument against institutional separation is related to the internal process by which agencies reach decisions. It is claimed that this process is unavoidably an interactive one. Different specialists are called on repeatedly for analysis and advice as an agency

identifies and considers new control options in attempting to reach a decision. Although this description may overstate the fluidity of internal agency deliberations, it captures something of their ad hoc character. Closely coupled with this argument is the necessity for agencies to retain scientific capability so that they can understand what a risk assessment means and how to use it in developing risk management strategies. Thus, even if risk assessment were performed outside the agency, a scientific staff representing many different disciplines would still be required, to ensure that an assessment would be interpreted and used correctly.

Other criticisms of proposals for risk assessment by a centralized panel stress the logistic difficulties of meshing independent risk assessment activities with the internal workings of different agencies. Experience suggests that it will be difficult for any risk assessment body to meet even generous time limits. Thus, agency decisions will probably be delayed by a requirement to consult, or refer issues to, such a body. A central panel also might become overburdened and cause additional delays. Critics of H.R. 638 and the AIHC proposal challenge the assumption that the regulatory agencies have reached inconsistent conclusions in evaluating various chemicals. The recent differences in the regulation of formaldehyde constitute a rare example of disparate treatment of the same chemical, and even this disparity may not betray basic disagreement over the interpretation of scientific data, as distinct from the degree of risk that justifies regulation. In the past, the agencies have often selected different control options or imposed different exposure limits for a given chemical, but these disparities have typically reflected differences in exposure (and thus in risk characterization) or differences in regulatory policy or statutory or administrative requirements; none of the current proposals addresses such differences.

CONCLUSIONS

The Committee was asked by the Congress to consider "the merits of an institutional separation of scientific functions of developing objective risk assessment from the regulatory process of making public and social policy decisions and the feasibility of unifying risk assessment functions." In this chapter, the Committee has addressed

these two issues and a third, related issue: the value of independent scientific review of agency risk assessments.

In its review, the Committee was sensitive to a number of considerations, including the scientific quality and regulatory relevance of the assessments performed. It also tried to ascertain how scientific and policy considerations were handled in the performance of risk assessment. To reach its conclusions, in the absence of accepted criteria for evaluating agency practices and proposals for change and in view of the sparseness of relevant empirical data, the Committee has relied on discussions with other persons knowledgeable and experienced in risk assessment activities, the limited available literature, and especially its own knowledge and experience in regulatory-agency risk assessments, as well as its review and analysis of past agency practices.

Value of Institutional Separation

1. Although organizational separation may help to ensure that risk management considerations do not influence the conduct of risk assessment, the degree of organizational separation that is optimal for individual agencies cannot be determined on the basis of the Committee's review.

Regulatory programs differ substantially in their degree of organizational separation. In the cases of NIOSH assessments that in the early 1970s were adopted by OSHA and NRC assessments relied on by agencies, the assessment function has been outside the regulatory agencies. At EPA, the risk assessment units in the Office of Health and Environmental Assessment of the Office of Research and Development prepare assessments for regulatory program offices that are organizationally under different assistant administrators. However, the Office of Toxic Substances does its own assessments, and several other program offices are responsible for their own exposure assessments. The risk assessments for the FDA'S Bureau of Foods are produced within the Bureau, but by an office distinct from offices responsible for formulating regulations and enforcement; since 1976, the Directorate of Health Standards Programs in OSHA has both performed risk assessments and formulated all early risk management options. Different agencies also have success

fully used different organizational arrangements for risk assessment. FDA, for example, has often called on NRC and NTP for assessments, but in other cases relied on its own staff. The Committee's review of different agency structures and procedures did not demonstrate that one particular structure produced risk assessments of superior quality and integrity. In addition, the Committee notes that, even if there were a clear finding that a particular arrangement works for a given agency or program, it would be extremely difficult (given the diversity in agency and program mandates, personnel needs, and histories) to justify a suggestion that that arrangement would best serve all agencies or programs

2. Organizational separation has several important drawbacks that are likely to be intensified with increasing degrees of separation.

There are several arguments against organizational separation. Separation of the risk assessment function from an agency's regulatory activities is likely to inhibit the interaction between assessors and regulators that is necessary for the proper interpretation of risk estimates and the evaluation of risk management options. Separation can lead to disjunction between assessment and regulatory agendas and cause delays in regulatory proceedings. Common sense suggests that increased separation would aggravate these drawbacks. In its review, the Committee observed these disadvantages when assessors and regulators were in different organizations (e.g., NIOSH and NRC). Another perceived drawback in extra-agency separation that was neither detected nor likely to emerge in the Committee's review is the erosion of scientific competence within agency staffs if risk assessments are routinely performed outside the agency. Also, any major organizational change may have a disruptive effect on agency performance; thus, such organizational changes are especially questionable when the benefits, if any, are unclear.

3. Organizational arrangements that separate risk assessment from risk management decision-making will not necessarily ensure that the policy basis of choices made in the risk assessment process is clearly distinguished from the scientific basis of such choices.

If risk assessment as practiced by the regulatory agencies were pure science, perhaps an organizational separation could effectively sharpen the distinction between science and policy in risk assessment and regulatory decision-making. However, many of the analytic choices made throughout the risk assessment process require individual judgments that are based on both scientific and policy considerations. The policy considerations in risk assessment are of a different character from those involved in specific risk management decisions and are generally common to all assessments for similar health effects. Thus, even when one has drawn the relatively obvious distinction between risk assessment and risk management, there remains the more difficult task of distinguishing between the science and policy dimensions of risk assessment itself. We believe that the latter distinction cannot be ensured or maintained through organizational arrangements. Given the inherent mixture of science and policy in risk assessment, organizational separation would simply move risk assessment policy into a different organization that would then have to become politically accountable. The Committee believes that other approaches are more likely to maintain the distinction between science and policy in risk assessment, most notably the development of and adherence to guidelines.

Value of Centralization

4. Common risk assessments performed primarily by scientists from all interested agencies on an ad hoc basis may capture the major advantages of centralization without the drawbacks that accompany permanent, extra-agency centralization.

An argument often advanced for centralization is that it might expedite and perhaps reduce the administrative costs of decision-making when two or more agencies contemplate regulation of the same substance. And if two or more agencies are going to regulate the same substance, there is much to be said for developing a system that facilitates production of a single, common risk assessment. This was one rationale for CPSC's decision to empanel a group of scientists to evaluate the carcinogenicity data on formaldehyde, and it argues in support of the central panels suggested in H.R. 638 and the American Industrial Health Council's proposal. Although the Com

mittee endorses government-wide consistency in risk assessment, it is less sanguine concerning the prospects of a permanent arrangement for such centralized risk assessment as contemplated by these proposals, in which the idea of centralized assessment is inextricably linked to extra-agency separation. The Committee concluded that extra-agency separation would have disadvantages that would offset any advantages.

The Committee did find, however, that agency scientists could collaborate to perform joint risk assessments on an ad hoc basis. Because agency scientists would perform an assessment, such an arrangement would avoid most of the drawbacks of extra-agency separation. The Committee looked at the Panel on Formaldehyde as an example of a centralized assessment group. In the Committee's view, the Panel functioned well and produced an assessment that has been accepted by the scientific community. The Panel's assessment has not produced parallel regulatory action among the agencies, and the Committee observed that similar risk assessments should not necessarily lead to similar regulatory decisions, which reflect considerations that often justify different risk management responses.

Use of Scientific Review Panels

5. Independent scientific review of agency risk assessments improves the scientific quality of the assessments and strengthens them against later challenge.

Agencies and programs with mandated peer review panels, such as EPA's Office of Pesticide Programs, which is required to submit to a Scientific Advisory Panel proposals to cancel or restrict pesticide use, produce final risk assessments in support of regulatory decisions that are generally of high scientific quality and are accepted by the public and the regulated parties. In contrast, the Committee found several cases in which mechanisms for peer review could be markedly improved: OSHA, which uses public comments to refine its risk assessments, rather than formal peer review; NIOSH, which has not had a mechanism to ensure that reviewers' comments are given appropriate consideration; and FDA's Bureau of Foods, which uses ad hoc panels to review its assessments (a procedure that unfortunately can be circumvented).

- Standing and continuing review panels that have mechanisms to maintain the independence of their members appear to be the most useful review bodies.

Continuity and independence of review panels help to ensure that such panels are sensitive to regulatory needs while retaining the necessary scientific objectivity. Examples of standing committees, such as the Scientific Advisory Panel in EPA, support this perception. Conversely, the Committee observed that short-lived or ad hoc groups, such as the Subcommittee on Airborne Carcinogens, often do not have sufficient time to develop a working relationship among panel members and that much of the time allotted to review is actually spent in clarifying individual versus panel viewpoints and understandings. Similarly, an ad hoc panel may not clearly understand its role in relation to the regulatory process. Thus, standing panels appear to be of greater value to the agency than ad hoc committees. Furthermore, the existence of a standing panel might encourage an agency to seek its advice more frequently.

Because it is important for review committees to be free to express their scientific judgments without concern for regulatory implications, panels that are formed in a manner that neither compromises nor appears to compromise their independence are more likely to improve ultimate risk assessments. The Committee observed that several review panels used by EPA already have a nomination process that places the responsibility for developing a slate of possible panel members outside the agency. Although the EPA Administrator makes the final selections of panel members, the fact that nominations come from outside the agency emphasizes the intent that EPA panels be independent and as free of agency influence as possible. A related point is that membership on EPA panels, and in fact on most review panels used by the regulatory agencies, rotates; members are usually selected for staggered, fixed terms (generally 3-4 years). This rotation itself reduces the likelihood that members will develop an institutional bias.

- Review panels are best qualified to give scientific advice when they are composed of scientists who are highly knowledgeable in the appropriate disciplines.

For carcinogenicity risk assessments, for example, some relevant disciplines would be toxicology, pathology, biostatistics, chemistry, and epidemiology. The Com

mittee believes that professional or organizational affiliation should not be used as a primary criterion in the determination of the makeup of a particular panel. That is, in contrast with the advisory panels used by OSHA, which are constituted to reflect balance among different affiliations and presumed biases, the Committee believes that scientific competence must be the primary factor determining panel membership if review panels are to be asked to give their advice on the scientific aspects of an agency's risk assessments. However, the Committee notes that panel members who understand the policy implications of their scientific judgments are more likely to be helpful to an agency's assessment process and that an attempt to balance viewpoints of scientifically qualified panel members may increase a panel's credibility.

- Review panels will be most effective if they have the authority to review agency risk assessments before announcement of the agency's intended regulatory actions, except in cases of emergency.

The Committee believes that review panels serving regulatory agencies should serve in an advisory capacity. That is, the judgments of a panel should not be binding on the agency. Nevertheless, the Committee also believes that the authority of agency review panels should be such that agencies must demonstrate that adequate consideration has been given to reviewers' judgments, and prior consultation with review panels helps to ensure this. Because announcements of intended actions or proposed regulations must be thoroughly developed and substantiated, review at the time of announcement or later is likely to be too late to influence an agency; although the regulation is only proposed, the decision of whether to act has, for all practical purposes, already been made. In the Committee's judgment, exceptions to this idea of prior review are appropriate in the case of emergency actions, such as suspension of pesticide registration. Risk assessments supporting such actions could be reviewed after the announced action.

- Independent panels with authority to review risk assessments for all agency regulatory decisions, including decisions not to act, are more likely to ensure that agency decisions rest on valid scientific grounds.

Panels with the authority to request the review of any agency risk assessment supporting a particular regulatory

decision will have a greater impact on agency decision-making. For example, if a panel can review only assessments referred to it by an agency, some agency decisions might not benefit from independent review of their scientific basis. This is especially likely if an agency has decided not to regulate. Such a decision may have considerable impact and should receive the same careful review as decisions to regulate. In addition, panels with the authority to request reviews can respond to suggestions for review from the public.

- Although most requirements of the Federal Advisory Committee Act are salutary, others may inhibit agency use of review panels.

The Committee believes that most provisions of the Act are beneficial and endorses such provisions as the requirement that advisory committees meet in public and provide advance notice of their meetings. However, the Act does impose requirements, some burdensome, for agency-created bodies that meet the definition of advisory committee. Notably, the Act requires that an advisory committee be formally chartered by an agency head and approved by the General Services Administration. This procedure has often proved cumbersome. Some agencies, such as FDA, lack independent chartering authority and thus require approval at the departmental level. In addition, procedures used by the General Services Administration for screening new committees have often imposed long delays, sometimes inspired by political concerns about committee membership or by resistance to the creation of new government "agencies." These legal requirements of the Act have caused some agencies to seek other ways of obtaining the views of scientific experts, especially when the issues involve single chemicals or tests. In such cases, regulators often confine their consultations to government scientists, who can be accessible immediately and, if necessary, for extended periods.

- Written reviews help to ensure agency consideration of scientific criticism.

A summary of a panel's review that is transmitted in written form and made available to the public will help to avoid confusion and to ensure agency consideration of the panel's comments. As mentioned earlier, in the absence of adequate mechanisms to ensure agency consideration of reviewers' comments, the comments might be

ignored, or the public might perceive that they are ignored. Putting its summary in writing should also ensure that the panel states its findings clearly and make it more likely that the agency will interpret its comments correctly.

Other Observations

6. Preparation of fully documented written risk assessments that explicitly define the judgments made and attendant uncertainties clarifies the agency decision-making process and aids the review process considerably.

When a fully documented written risk assessment is not produced before an agency's decision to regulate or not to regulate, it is difficult to understand the process by which an agency made its assessment. The Committee believes that the creation of such a document encourages public understanding of and respect for agency procedures and provides a basis for review by a scientific advisory panel. Furthermore, a detailed risk assessment document that clearly identifies the inference options chosen in the assessment and explains the rationale for those choices will help to maintain a sharper distinction between science and policy in the assessment of risk and will guard against the inappropriate intrusion of risk management considerations.

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IV

Recommendations

The Committee has reviewed federal risk assessment for hazards to public health, particularly for chemically induced cancer, and has presented its findings concerning the nature of risk assessment, the nature and utility of risk inference guidelines, and the effects of alternative organizational arrangements on risk assessment. The Committee's review leads to the general observation that the process of risk assessment, as performed by and for federal regulatory agencies, has been developing rapidly in recent years, both with respect to its scientific basis and with respect to the agencies' organizational arrangements. Change this rapid is bound to lead to misunderstanding about the use of risk assessment in regulatory policy-making, particularly if some misconstrue risk assessment to be a strictly scientific undertaking. Much of the criticism of risk assessment stems from dissatisfaction with regulatory outcomes, and many proposals for change are based largely on the unwarranted assumption that altering the administrative arrangements for risk assessment would lead to regulatory outcomes that critics will find less disagreeable. Because risk assessment is only one aspect of risk management decision-making, however, even greatly improved assessments will not eliminate dissatisfaction with risk management decisions.

The Committee believes that the basic problem with risk assessment is not its administrative setting, but rather the sparseness and uncertainty of the scientific knowledge of the health hazards addressed. Reorganization of the risk assessment function will not create the data and underlying knowledge that assessors need to make risk assessments more precise. We hold that the most productive path to a solution has three parts:

- Implementation of procedural changes that ensure that risk assessments take full advantage of the available scientific knowledge while maintaining the diverse organizational approaches to administration of risk assessment needed to accommodate the varied requirements of federal regulatory programs.
- Standardization of analytic procedures among federal programs through the development and use of uniform inference guidelines.
- Creation of a mechanism that will ensure orderly, continuing review and modification of risk assessment procedures as scientific understanding of hazards improves.

The Committee offers in the following pages 10 recommendations whose implementation it believes will meet these general objectives.

IMPROVING RISK ASSESSMENT THROUGH PROCEDURAL CHANGES

Recommendation 1

Regulatory agencies should take steps to establish and maintain a clear conceptual distinction between assessment of risks and the consideration of risk management alternatives; that is, the scientific findings and policy judgments embodied in risk assessments should be explicitly distinguished from the political, economic, and technical considerations that influence the design and choice of regulatory strategies.

Although the Committee concludes that risk assessment cannot be made completely free of policy considerations, it also believes that policy associated with specific risk management decisions should not influence risk assessment unduly. Risk assessment and risk management involve different goals, kinds of expertness, and operating principles. The goal of risk assessment is to describe, as accurately as possible, the possible health consequences of changes in human exposure to a hazardous substance; the need for accuracy implies that the best available scientific knowledge, supplemented as necessary by assumptions that are consistent with science, will be applied. The ultimate aim of risk management is to evaluate tradeoffs between health consequences and other effects of specific regulatory actions; this evaluation includes the application of value judgments to reach a policy decision.

Experience shows the difficulties that can arise from a blurring of the distinction between the two elements. If risk management considerations (for example, the economic or political effects of a particular control action for a particular chemical) are seen to affect either the scientific interpretations or the choice of inference options in a risk assessment, the credibility of the assessment inside and outside the agency can be compromised, and the risk management decision itself may lose legitimacy. Indeed, such consequences can flow from the mere perception, as well as the fact, of such influences. Each regulatory agency should commit itself to safeguarding the distinction between the processes of risk assessment and risk management. One among several suggestions for accomplishing this safeguarding is to restructure the formal organization, separating an agency's or program's risk assessment staff from its policy-making staff, possibly by establishing a separate risk assessment unit outside the agency. The Committee does not, however, recommend that agencies use any particular organizational arrangement for risk assessment. One might surmise that separating the staffs would help to reduce the likelihood that risk management considerations will influence risk assessment, but our survey of agency structures provided no clear evidence that such an influence was related to the degree of administrative separation.

Formal separation has disadvantages that must be balanced against its value in maintaining a distinction between risk assessment and risk management. Risk assessment and risk management functions are analytically distinct, but in practice they do—and must—interact. Organizational arrangements that completely isolate risk assessors from regulatory policy-makers may inhibit important communication in both directions. For example, to complete risk characterization, risk assessors must know what policy options are to be used to calculate alternative projected exposures, and new options may develop as the risk management process proceeds. Moreover, direct communication with the risk assessors is desirable to ensure that the regulatory decision-maker understands the relative quality of the available scientific evidence, the degree of uncertainty implicit in the final risk assessment, and the sensitivity of the results to the assumptions that have been necessary to produce the assessment. Such separation could also impair the risk manager's ability to obtain assessments that are timely and in a useful form. The advisability of organizational

separation hinges on comparison of its benefits and costs in particular agencies and programs.

Because drawbacks are likely to be most pronounced in the case of extra-agency separation, the Committee does not believe that it is appropriate to remove the risk assessment function and place it in an organization completely separated from the regulatory agencies, as is contemplated in the AIHC proposal and H.R. 638. This judgment is supported by the conclusion that the benefits of increased separation are uncertain and that the disruption and confusion caused by reorganization could be considerable.

Measures other than organizational separation can ensure the distinction between the assessment of risk and the consideration of risk management alternatives. These measures include the practice of preparing written risk assessments (Recommendation 2), arranging for independent peer review (Recommendation 3), and adhering to uniform guidelines for risk assessment (Recommendations 5 through 9).

Recommendation 2

Before an agency decides whether a substance should or should not be regulated as a health hazard, a detailed and comprehensive written risk assessment should be prepared and made publicly accessible. This written assessment should clearly distinguish between the scientific basis and the policy basis for the agency's conclusions.

Although agencies commonly perform risk assessments before they take regulatory actions, the written assessments that are prepared vary in coverage, amount of explanatory detail, format, and completeness to an extent that limits their use as instruments of communication. The Committee believes that the matters addressed are so important and the consequences so far-reaching that a written risk assessment should be prepared for every significant regulatory decision and that each should be a clear, detailed, and comprehensive account of the analysis performed. A written assessment should describe the volume and weight of scientific evidence to help to clarify the scientific and policy bases for regulatory decisions.

The written assessment should be made accessible to the public at a time and in a form that facilitates public participation in any attendant risk management decision.

The Committee believes that the requirement to prepare a written assessment imposes a salutary discipline that, for several reasons, will improve the performance of risk assessment. First, the requirement to prepare a comprehensive written assessment will encourage the agency to explain how each component of the assessment was treated; that should minimize the likelihood that risk management considerations will, unnoticed, affect the outcome of the assessment. Second, a written assessment can help to distinguish the factual basis of a risk assessment from inferences drawn where there is a lack of scientific consensus; this distinction will facilitate scientific review of the risk assessment, document the scientific basis of the assessment for outside observers, and acquaint the regulatory decision-maker with the relative completeness of the scientific evidence. Third, it will aid communication among specialists working on different parts of the assessment. Fourth, the existence of an explicit description should simplify the conduct of later assessments of the same chemical, if additional scientific evidence comes to light or other regulatory programs review the same substance. Finally, written risk assessments will be useful to institutions that oversee regulatory agencies, notably Congress and those responsible for judicial review. It is important, however, that the format and scope of written assessments not become an independent basis for legal attack.

Content and Form

An agency's written risk assessment should set forth in detail the nature and quality of the relevant scientific evidence concerning the substance in question and should cover all relevant components of risk assessment. It should reflect attention to any applicable guidelines relied on in interpreting the evidence, so that a reader can ascertain what inference options were used, and should describe the scientific rationale for any departures from methods prescribed in such guidelines. If the choice of inference options is not governed by guidelines, the written assessment itself should make explicit the assumptions used to interpret data or support conclusions reached in the absence of data. The document should acknowledge gaps and uncertainties in available information.

An agency's written assessments are likely to prove most useful if they follow a consistent format, so that readers, once familiar with the format, can use them efficiently. We believe that each program or agency can establish a uniform structure for its written assessments, and we hope that similarity, if not uniformity, will be possible in written assessments prepared throughout the government.

Actions Covered

This recommendation is not intended to apply to the risk posed by every substance, use, or exposure that engages an agency's attention. It is intended to apply to agency decisions concerning important human exposure to a hazard. Such decisions would include (but not be limited to) establishment of an occupational safety and health standard by OSHA, cancellation by EPA of the federal registration of a pesticide to which there is widespread human exposure, and EPA promulgation of limits for an air or water pollutant. The categories of actions covered by this recommendation could be defined precisely only after detailed statutory analysis. EPA appears to have had satisfactory experience with the practice of classifying its regulations as "major" (those with very large economic and other effects that require an extensive regulatory analysis and formal review by the Office of Management and Budget), "significant" (a larger category defined by internal EPA criteria), and "minor" (a similarly large group of routine and technical actions). We suggest that EPA prepare a written assessment for every major and significant action, and we encourage other agencies to devise similar methods of identifying which regulatory actions require written assessments.

An agency's decision to refrain from regulation can often have important consequences, both for health and for the economy, and such decisions should rest on accurate, objective assessments of risk. The denial of a petition to act on a chemical to which exposure is extensive is an example. When an agency is confronted with choosing between limiting exposures to a substance and taking some lesser action and there is serious dispute over the character or extent of the risk posed, a written assessment is advisable.

Recommendation 3

An agency's risk assessment should be reviewed by an independent science advisory panel before any major regulatory action or decision not to regulate. Peer review may be performed by science panels already established or authorized under current law or, in their absence, by panels created for this purpose.

- If an agency's workload is substantial, a standing advisory panel (or panels) should be established to review its risk assessments; otherwise, ad hoc panels should be established on a case-by-case basis.
- Panel members should be selected for their scientific or technical competence.
- The appointment of members should be the responsibility of each agency director, but nominations from the public and scientific organizations should be invited, unless current law prescribes another procedure.
- Panels should provide to the referring agencies written evaluations of agency risk assessments, and the evaluations should be available for public inspection.

This recommendation endorses outside peer review of agency risk assessments. Such review should contribute to the important distinction between risk assessment and risk management, because risk management information would be excluded from the review; should improve the scientific quality of the assessments through the process of criticism and response; and should increase the credibility of agency assessments. The practice of preparing written risk assessments will facilitate the review process.

The peer review function that we visualize is already evident in some agencies. We believe that a single approach would not fit all contexts, but that any mechanism for scientific peer review should meet the general criteria described below.

Panel Form

The review function we recommend could be performed effectively by an appropriately qualified standing panel of independent scientists that is responsible for reviewing agency assessments of a particular class of hazards. Any agency program responsible for a large number of

compounds to which humans are exposed in large amounts seems to be an appropriate candidate for a standing scientific review panel, but some programs may deal with so few chronic health hazards that a standing panel is not warranted. The Committee specifically contemplates that the review function recommended here can be performed by panels already available to several agency programs.

Panel Composition and Selection

Members of a scientific review panel should be selected for their competence in fields relevant to the assessment of risks of the kind being evaluated. In our judgment, employees of private business organizations, members of environmental groups, and government research or regulatory agency employees should not necessarily be disqualified; but no panel members should be employees of the agency whose risk assessments are to be reviewed, nor should any members participate in the review of substances in which they or their employers have substantial economic or other interests or on whose risks they or their employers have publicly taken a position. It is important to safeguard both the reality and the appearance of complete objectivity for each review.

We contemplate that, as is common for existing panels, the appointing official would be the head of the agency whose risk assessments are to be reviewed. Such an arrangement could be thought to jeopardize a panel's independence from the agency, particularly in cases in which it is known which chemicals the panel will review. Accordingly, each agency should establish procedures for obtaining nominees for panel membership whose objectivity is ensured. For example, some current procedures call for agency selection of members from lists of nominees provided by the President of the National Academy of Sciences and by the Directors of the National Institutes of Health and the National Science Foundation. We see no magic in any particular nomination process. The important objective is a process that, first, ensures that panel members are selected for their training and experience in relevant fields; second, prevents the appointing official from forming a panel that will produce (or appear to produce) a predetermined result; and, third, operates expeditiously. We recommend that this process include an opportunity for members of the public to nominate persons for panel membership.

Panel Functions

Our recommendation contemplates that, in a typical case, the responsible agency will have prepared a written assessment of the risk posed by a substance. The independent scientific panel would be asked to review that assessment for comprehensiveness, scientific accuracy, and consistency with any applicable risk assessment guidelines. If such guidelines are flexible, an important panel function will be to ensure that departures from the inference options favored by the guidelines are justified on scientific grounds. In performing this role, the panel should, if it desires, have access to all the data available to the agency, including those on which the agency's analysts relied, as well as the agency's written assessment. The panel should subject the agency's risk assessment to such scrutiny as the members find necessary to satisfy themselves that it is, with or without revisions, as complete and objective as available data permit. The panel should provide a written evaluation of the agency's risk assessment, including recommendations for revision, if appropriate. This evaluation should be available for public examination by the time the agency initiates public proceedings to alter human exposure to the substance in question for example, when the agency issues a notice of proposed rule-making.

Panel Agenda

Independent review of agency risk assessments is designed to ensure the integrity and quality of the scientific bases for regulatory decisions affecting human health. Therefore, the Committee recommends that every action, including a decision not to regulate, that requires a written risk assessment be available for independent scientific review. A scientific review panel's agenda may also include risk assessments for other decisions of interest to panel members, or its review could be initiated after a request by a third party. In the latter case, panels should have the authority to decide whether or not to respond to such requests for review. In general, the Committee expects that the panels would exercise discretion in invoking their authority to review assessments for routine, minor actions.

Timing of Review

Independent scientific review of agency risk assessments should occur before an agency commences the public process leading to regulatory action. The purpose is to expose the agency's initial assessment of the risk posed by a substance to expert scrutiny at a time when review can influence the agency's course of action. Experience suggests that agencies are less receptive to criticism of the basis of their actions after they have announced a proposed course of action. Furthermore, although independent review can sometimes forestall misguided regulatory actions even after they are initiated, prior review of such actions may help to avoid serious damage to agency credibility and unnecessary costs to private interests that would be adversely affected by public proposals for regulatory action. We recognize an important exception to our general recommendation of precaution peer review. Several statutes expressly empower agencies to act in an emergency to curtail human exposure to a substance that poses a serious health risk. Agencies have also devised informal procedures to effect immediate protection of humans exposed to dangerous substances in other contexts. Our recommendation is not intended to cast doubt on the legitimacy of such authority or to impede its appropriate exercise. When an agency concludes that a hazard warrants immediate regulatory action to limit human exposure, it should be able to take action consistent with existing law without first going through the review process that we recommend. Promptly thereafter, however, the agency should submit its written risk assessment for independent review in accordance with the procedures outlined here.

Weight of Panel Evaluation

A scientific review panel's critique of an agency's risk assessment should not be binding; that is, the agency should not be obliged to revise its risk assessment if the panel regards it as deficient. Agencies have a responsibility to state the basis of their actions, and the authority for their actions must remain their own. Serious panel criticism, however, would in practice cause any agency at least to reconsider, and ordinarily to revise, its risk assessment. The agency should discuss any important criticisms of its assessment in its proposed regulatory action, and its response to a panel's criti

cisms would be an appropriate subject for public comment, as well as a possible basis for judicial challenge to any final action.

We believe that an important benefit of peer review occurs before the review begins: risk assessors who expect an assessment to be subjected to serious scrutiny by eminent qualified reviewers are likely to be more careful and clear about the use and limits of scientific evidence.

Federal Advisory Committee Act

The Federal Advisory Committee Act imposes many salutary requirements on panels established to advise federal agencies, including notably the requirement that panel meetings be held in public. But the Act's requirement that new advisory committees be chartered by the General Services Administration imposes substantial delays and its requirement that panel meetings be announced in the Federal Register at least 15 days in advance can markedly slow a panel's work. Consideration should be given to modifying both requirements or exempting such panels from the Act, as Congress did for CPSC's Chronic Hazard Advisory Panels.

Recommendation 4

When two or more agencies share interest in and jurisdiction over a health hazard that is a candidate for regulation by them in the near term, a joint risk assessment should be prepared under the auspices of the National Toxicology Program or another appropriate organization. Joint risk assessments should be prepared primarily by scientific personnel provided by the agencies and assisted as necessary by other government scientists.

This recommendation endorses coordination in assessing the risks of chemicals that are likely candidates for regulation by two or more agencies. Although all the end uses of a substance may fall within the jurisdiction of one agency (such as FDA for a food additive), exposures occurring during production, transportation, and distribution usually are within other agencies' jurisdictions. Thus, chemicals that pose a hazard to human health are at least theoretically subject to regulation by two or more

federal agencies. The Committee agrees with proponents of the centralization of risk assessment responsibilities that the agencies involved should operate on the basis of a common assessment of the substance's risks. However, the Committee differs with respect to the method for achieving this end.

Actions Covered

Our recommendation does not call for the performance of a joint risk assessment in every instance in which a substance potentially falls within the jurisdiction of two or more agencies; we limit our proposal to circumstances in which assessment by more than one agency is likely in the near future. This limitation has two rationales. First, substantial risk may be associated with routes of exposure of concern to only one agency. Under such circumstances, it would be unreasonable to invest time and resources to establish an interagency panel of scientists. Second, even if different types of exposure entail risks, a substance may legitimately rank low in priority for one agency and high for another.

Placement and Procedures

The approach we visualize is similar to that followed in 1980, when the Interagency Regulatory Liaison Group, at the suggestion of CPSC, sought the assistance of the National Toxicology Program to examine the carcinogenicity of formaldehyde. The Program formed an ad hoc panel that consisted entirely of government scientists, including some from EPA, OSHA, and FDA.

We suggest that the National Toxicology Program be the usual vehicle for coordinating preparation of joint risk assessments. The National Toxicology Program has been in operation for several years and, in the Committee's judgment, has performed capably as coordinator of federal toxicologic research. It has displayed an ability to command the service of the government's best scientists. And it has developed effective working relationships with the regulatory agencies, which have become accustomed to looking to it for assistance in evaluating substances that are candidates for regulation.

We expect that suggestions for establishment of an interagency task force to evaluate a hazard will come

from the interested regulatory agencies. The personnel assigned to assemble the relevant data and perform the assessment could include scientists from the interested regulatory agencies, including the initiating agencies, and scientists from government research organizations, such as the National Institute of Environmental Health Sciences, the National Cancer Institute, and the National Center for Toxicological Research. The Committee recommends that task forces follow the same guidelines used by the regulatory agencies. Joint risk assessments should be subjected to independent scientific review.

For reasons presented in the discussion of Recommendation 1, the Committee believes that such an ad hoc approach is preferable to creation of a centralized risk assessment body.

IMPROVING RISK ASSESSMENT THROUGH UNIFORM INFERENCE GUIDELINES

Recommendation 5

Uniform inference guidelines should be developed for the use of federal regulatory agencies in the risk assessment process.

In the Committee's judgment, the development of uniform inference guidelines is feasible and desirable. However, the Committee emphasizes that guidelines cannot provide a formula for automatically calculating risk from available data; case-by-case scientific interpretation will still be crucial, and risk assessments must reflect experts' characterizations of the quality of the data and of the uncertainty associated with the final assessment.

Adherence to uniform guidelines has several advantages over ad hoc performance of risk assessments. Guidelines could help to separate risk assessment from risk management considerations, improve public understanding of the process, foster consistency, and prevent oversights and judgments that are inconsistent with current scientific thought. The development and application of guidelines would help to focus discussion by the public and the scientific community on the generic issues of risk assessment, outside the sometimes charged context of particular regulatory decisions. Such discussion could stimulate research interest and lead to evolutionary improvement in the guidelines and thus in the quality of

risk assessment—improvement that would not occur if risk assessments were performed on an ad hoc basis. Guidelines also provide an efficient means to ensure the quality and relevance of data generated in new bioassay, epidemiologic, and other pertinent studies on the toxicity of particular chemicals, thus improving the scientific data base for future risk assessments of those chemicals. Guidelines can also help regulated parties to know in advance the criteria that agencies will apply in evaluating substances. Industry would benefit if all federal agencies used the same guidelines. Furthermore, uniform federal guidelines could help to harmonize the current development of risk assessment methods by an increasing number of state programs.

Uniform guidelines should be prepared for hazard identification, dose-response assessment, and risk characterization. Government-wide guidelines for exposure assessment may be impractical, and this aspect of risk assessment is treated separately in Recommendation 9.

The Committee is aware of several arguments to the effect that uniform guidelines could have adverse effects. We believe, however, that well-designed and carefully applied guidelines will minimize these disadvantages.

Recommendation 6

The inference guidelines should be comprehensive, detailed, and flexible. They should make explicit the distinctions between the science and policy aspects of risk assessment. Specifically, they should have the following characteristics:

- They should describe all components of hazard identification, dose-response assessment, and risk characterization and should require assessors to show that they have considered all the necessary components in each step.
- They should provide detailed guidance on how each component should be considered, but permit flexibility to depart from the general case if an assessor demonstrates that an exception is warranted on scientific grounds.
- They should provide specific guidance on components of data evaluation that require the imposition of risk assessment policy decisions and should clearly distinguish those decisions from scientific decisions.

- They should provide specific guidance on how an assessor is to present the results of the assessment and the attendant uncertainties.

Distinguishing Science from Policy

A frequent deficiency of agency risk assessments is the failure to distinguish between scientific and policy considerations in risk assessment. Critics contend that the results of risk assessment are often seen as scientific findings by regulators and the public, whereas in fact they are based in part on other considerations. The Committee believes that guidelines can lead to risk assessments that clearly delineate the limits of current scientific knowledge and the policy basis for choosing among inference options.

Comprehensive and Detailed Nature

Comprehensive, detailed guidelines are needed to delineate risk assessment as a process distinct from risk management. Comprehensive guidelines are those which address all components of risk assessment that are subject to generic treatment. Detailed guidelines are those which provide substantial supplementary scientific discussion of each component. Such discussion helps to reduce the possibility that analysts will misuse guidelines as cookbook instructions and helps analysts to anticipate special conditions for which particular inference options are appropriate or inappropriate.

Broad statements of principle are inadequate, because they leave components undefined and may permit excessive discretion in particular cases. An explicit, comprehensive statement has the advantages of improving public understanding of government risk assessment and of assisting regulated parties to anticipate government actions.

Another reason for specifying comprehensive, detailed guidelines is that they hold the greatest promise of preventing inconsistency within and among agencies. At numerous points in a risk assessment, different risk assessors may select different (but scientifically valid) inference options; guidelines should specifically address each of these. A related advantage is an improvement in quality control that could occur if all assessors were

required to consider the broad range of issues addressed in such guidelines; that would decrease the likelihood that important considerations would be neglected or that uninformed judgment would occur.

Flexibility

The Committee espouses flexible guidelines. Rigid guidelines, which permit no variation, might preclude the consideration of relevant scientific information peculiar to a particular chemical and thus force assessors to use inference options that are not appropriate in a given case. Also, rigid guidelines might mandate the continued use of concepts that become obsolete with new scientific developments. Large segments of the scientific community would undoubtedly object to such guidelines as incompatible with the use of the best scientific judgment for policy decisions.

Flexibility can be introduced by the incorporation of default options . The assessor would be instructed to use a designated (default) option unless specific scientific evidence suggested otherwise. The guidelines would thus permit exceptions to the general case, as long as each exception could be justified scientifically. Such justifications would be reviewed by the scientific review panels and by the public under procedures described above. Guidelines could profitably highlight subjects undergoing relatively rapid scientific development (e.g., the use of metabolic data for interspecies comparisons) and any other components in which exceptions to particular default options were likely to arise. They should also attempt to present criteria for evaluating whether an exception is justified.

Presenting the Results of the Assessment

Conclusions based on a large number of sequential, discretionary choices necessarily entail a large, cumulative uncertainty. The degree of uncertainty may be masked to some extent when, in the final form of an assessment, risk is presented as a number with an associated measure of statistical significance. If they are to be most instructive to decision-makers, assessments should provide some insight into qualitative characteristics of the data and interpretations that may impute more or less certainty to the final results.

Recommendation 7

The process for developing, adopting, applying, and revising the recommended inference guidelines for risk assessment should reflect their dual scientific and policy nature:

- An expert board should be established to develop recommended guidelines for consideration and adoption by regulatory agencies. The board's recommended guidelines should define the scientific capabilities and limitations in assessing health risks, delineate subjects of uncertainty, and define the consequences of alternative policies for addressing the uncertainties.
- The expert board's report and recommendations should be submitted to the agencies responsible for regulating the hazards addressed by the guidelines for their evaluation and adoption. The agencies, perhaps with central coordination, should, when possible, choose a preferred option from among the options that are consistent with current scientific understanding. The procedures for adoption should afford an opportunity for members of the public to comment.
- The process followed by the government for adoption of inference guidelines should ensure that the resulting guidelines are uniform among all responsible agencies and are consistently adhered to in assessing the risks of individual hazards.
- The resulting uniform guidelines should govern the performance of risk assessments by all the agencies that adopt them until they are re-examined and revised; they should not prevent members of the public from disputing their soundness or applicability in particular cases. In short, the guidelines should have the status of established agency procedures, rather than binding regulations.
- The guidelines should be reviewed periodically with the advice and recommendations of the expert board. The process for revising the guidelines, like the process for adoption, should afford an opportunity for comment by all interested individuals and organizations.

Inference guidelines for risk assessment are based largely on science, but other considerations are involved in components with substantial scientific uncertainty. For these, the choice among inference options can have substantial policy ramifications. Thus, we recommend a

two-step process in which a board of experts recommends guidelines and provides scientific commentary on available inference options and then the government adopts final guidelines based in part on the board's recommendations.

The Board and Its Role

The recommended guidelines should be developed by a congressionally chartered board of experts who are independent of regulatory policy-making. We describe this board, its placement, and other functions that it can serve in Recommendation 10. In general terms, the board should be permanent, should represent professional excellence on a national scale, and should have facility with issues that have policy ramifications. We see advantages in locating the board outside the government.

The board's role is mainly scientific. It should define the components of risk assessment and describe the scientific basis for each. When it finds general scientific agreement on the proper inference option for a component, it should designate that option in a recommended guideline. When the board finds no general scientific agreement on the available inference options, it should recommend against the use of options that are scientifically unsupportable and comment on the relative strength of the scientific support for the options that remain.*

Agency Adoption

The Committee envisions that the second step in the establishment of guidelines will be in the hands of the

* Some members of the Committee believe that the board should also be encouraged in such cases to recommend the option that it judges to have the most scientific support, as long as the board clearly indicates that such choices are based on members' informed scientific judgment, not on general agreement in the scientific community. Other Committee members believe that such recommendations would imply scientific certainty where none exists and thus would result in scientists' improperly recommending policy on the basis of their subjective judgments.

government. The choice of guidelines is, ultimately, the responsibility of duly elected or appointed public officials, and public review and comment on the proposed guidelines should be completed before they are adopted. The Committee emphasizes that, to be most useful, the final guidelines should prescribe default options for all components of risk assessment. Thus, the second step should further limit the inference options available to the agencies, even for components in which the board found that no single option could be chosen on scientific grounds. In that case, full consideration should be given to the board's comments on the merit of the scientific support that is available for each option.

It is important that the process result in a timely, uniform set of inference guidelines to be used by all agencies. We thus see advantage in coordination of the agencies' adoption of guidelines by a single, central authority such as the Office of Science and Technology Policy, or by a mechanism designated by Congress.

The Committee believes that adopting the guidelines as established procedures, rather than as formal regulations, would have several important advantages: it would allow guidelines to be adopted and amended more easily; it would bind the agencies to adhere to the guidelines until they were reviewed and revised (thus fostering predictability and consistency—any agency's failure to comply with its own guidelines could be noted by independent scientific review panels and could be cited as grounds for interested parties' legal appeal of an associated regulatory decision); and it would permit members of the public to advocate new or alternative approaches to risk assessment.

Joint risk assessments performed by interagency task forces should be governed by the guidelines that emerge from this process.

Uniformity

The Committee has presented its case for uniformity in guidelines: consistency in the conduct of risk assessment reduces the appearance of unfair and inconsistent regulatory policies, improves priority-setting among regulators' programs, increases public understanding, and provides coherence for those subject to various regulatory authorities. A frequent argument against government-wide guidelines is that different agencies have statutory respon

sibilities that reflect different social policies and therefore require different approaches to risk assessment. This argument reflects a misunderstanding of the purpose of guidelines. An agency would remain free to incorporate whatever social judgments are embodied in its mandate when deciding whether and how to regulate. Such risk management choices can be made independently of and after the completion of a risk assessment. Thus, two agencies could use the same risk assessment of a substance, but regulate it differently on the basis of statutory or policy criteria applied after risk assessment.

Periodic Review

The scientific basis of risk assessment is evolving rapidly. Guidelines must continue to evolve to accommodate scientific innovations and theories. By their very nature, guidelines themselves will help to foster evolutionary improvements by defining generic principles of risk assessment and focusing debate and empirical research on these principles.

Furthermore, new public perceptions of risk occur, and guidelines will evolve in response to these changes as well. For example, attitudes about the practicality of the outright elimination of carcinogenic risk as a regulatory goal have changed in the last decade. New methods of quantitative risk assessment have developed, and public discussions have increasingly focused on that field. These changes can be expected to continue, so regular periodic review of guidelines appears to be essential. Such review should follow the same procedures recommended for the initial guidelines, including ultimate agency adoption after public comment.

Recommendation 8

The Committee recommends that guidelines initially be developed, adopted, and applied for assessment of cancer risks. Consideration of other types of health effects should follow. It may not yet be feasible to draw up as complete a set of inference guidelines for some other health effects. For these, defining the extent of scientific knowledge and uncertainties and suggesting methods for dealing with uncertainties would constitute a useful first step.

The Committee believes that guidelines for carcinogenic risk assessment should be drawn up first: both because cancer is perceived as a major public-health hazard and because there is considerable experience with carcinogenic risk assessment from which to draw. Several guideline documents for carcinogenic risk assessment have already been produced, and review of these documents and of their history should provide a useful point of departure.

However, the other health effects that result from exposure to hazardous substances are equally amenable to prevention by regulatory action. Guidelines are desirable for these types of effects, which include mutagenicity, reproductive and teratogenic effects, neurotoxicity, and behavioral changes. Less information (and, in some cases, less knowledge of causal mechanisms) is usually available on these effects. In fact, in some situations where the knowledge base is less adequate than in cancer, stipulated methods for handling scientific uncertainty may be even more important. Risk assessments for cancer are likely more frequently to engage the problems of evaluating data on exposure of experimental animals, whereas many other health effects will require greater reliance on epidemiologic evidence.

The Committee believes that the absence of guidelines for a health effect is not a justification for agency failure to perform risk assessments or to regulate on a case-by-case basis.

Recommendation 9

Agencies should develop guidelines for exposure assessment. Because of diverse problems in estimating different means of exposure (e.g., through food, drinking water, and consumer products), separate guidelines may be needed for each.

Operating assumptions are needed to estimate exposures when direct measurements cannot be obtained. Examples of cases in which such estimates would be important are the projection of exposure to new chemicals and determination of the exposure reduction that would result from implementation of a particular control option. In only a few narrow cases (e.g., food additives) have general guidelines been developed for exposure assessment.

Although they are no less important than techniques for hazard identification and dose-response assessment,

exposure assessment techniques have not been the subject of major scientific debate and scrutiny. For example, if exposure were known more accurately, priority-setting for testing new chemicals or for initiating regulation of one of a group of chemicals could be organized on a more rigorous basis; consideration of both the apparent potency and the estimated exposure would be factored into such decisions.

Exposure assessment guidelines that are uniform across federal programs may not be feasible, because of the diversity of media that must be addressed and the large variation in exposures. Medium-specific exposure models (such as dispersion models for air, water, and soil) are used by programs in the agencies with various degrees of sophistication and validation. Each agency or each program in an agency should develop medium-specific guidelines to stimulate evolutionary improvement, increase consistency and predictability, and isolate the choice among inference options from inappropriate risk management considerations. Two or more programs that deal with a given medium of exposure should use the same guidelines.

Agencies should make their proposed exposure assessment guidelines available for public comment and should subsequently issue final guidelines as established procedures.

A CENTRAL BOARD ON RISK ASSESSMENT METHODS

Recommendation 10

The Committee recommends to Congress that a Board on Risk Assessment Methods be established to perform the following functions:

- To assess critically the evolving scientific basis of risk assessment and to make explicit the underlying assumptions and policy ramifications of the different inference options in each component of the risk assessment process.
- To draft and periodically to revise recommended inference guidelines for risk assessment for adoption and use by federal regulatory agencies.
- To study agency experience with risk assessment and evaluate the usefulness of the guidelines.
- To identify research needs in the risk assessment field and in relevant underlying disciplines.

To avoid possible misunderstanding of the role of the Board, the Committee stresses the limitations on proposed Board activities. The Board would not perform or review individual risk assessments, nor would it adjudicate disputes arising from regulatory actions related to specific substances. Thus, the Board as envisioned would not perform functions contemplated by the AIHC proposal or H.R. 638. A central board of distinguished expert advisors is not well-suited to such day-to-day responsibilities. Furthermore, we believe strongly that it would be inappropriate to remove such essential analytic functions from the responsible agencies and that it would be wasteful to duplicate agency activities.

The Board would make its contributions through discussion of contending scientific positions, preparation of recommended uniform guidelines, and fostering of advancement of the field. It would fill a need for a prestigious, independent locus of activity for improving the understanding of generic issues in both the scientific basis and the federal practice of risk assessment. Current ad hoc approaches too often color debate on general issues with the implications for particular, often contentious, risk management decisions. We expect that Board activities would improve the scientific performance of the agency processes and, in conjunction with other mechanisms we recommend, achieve greater objectivity and consistency and better public understanding of risk assessment. The Board would be the body to which agencies, agency review panels, and others would turn both for periodic recommendations of guideline revisions and for information on the evolving art of risk assessment.

Board Functions

We foresee four major functions for the Board. The first two, scientific review and development of recommended guidelines, would pursue the process described above for the initial generation of inference guidelines (Recommendation 7). The drafting of guidelines by the Board would ensure that guidelines benefit from the best available scientific knowledge and judgment. After recommended guidelines for a particular health effect were prepared and referred to the agencies for review and adoption, the Board would probably find it useful to continue its activity in the review of scientific developments relevant to risk assessment for that effect.

The Board's third function would involve observation of and research into federal experience with risk assessment generally and review of the usefulness of guidelines. A major purpose would be to acquaint the Board with ways of improving the guidelines in later periodic reviews.

As a fourth function, the Board would identify the key scientific research needs in health risk assessment. Preparation of guidelines would put the Board in an ideal position to understand which of the many inference options needed to cover gaps in scientific understanding are most important and are amenable to study. The policy difficulties in regulating chronic health hazards can be resolved only if uncertainty in the scientific basis of assessments is reduced. Board activities could take such forms as advising funding agencies on research priorities, commissioning survey papers to synthesize recent scientific findings, and sponsoring conferences or special publications on particularly apt scientific questions or on matters that are important to risk assessment, but have been neglected by the scientific community. In addition, the Board's experience would place it in an ideal position to assess whether and how toxicologic research on particular chemicals could be better tailored to the analytic needs of future risk assessors. For example, many current testing procedures were designed for the narrow purpose of hazard identification, and adjustments in these procedures could lead to more definitive dose-response assessments.

The Committee believes that the responsibilities of the Board could be discharged by a group of volunteer experts that convened monthly for 1-2 days.

Organizational Placement

The proper placement of the Board would be crucial to its prospects for success. There are four criteria for identifying appropriate locations: professional excellence, facility with studies having substantial policy ramifications, permanence, and independence.

Professional excellence is important because the Board's recommended guidelines, as well as its other work, should be based on the best available science; the Board should be able to attract the best talent in the nation. Facility with difficult policy issues is important because risk assessment is not a strictly scientific undertaking, and it would be crucial for the Board to

conduct its work competently and with full understanding of the policy process. Placement in a permanent, existing organization is advisable because the Board should be able to begin its work quickly and remain stable in order to conduct periodic revisions of guidelines. Independence is needed to provide credibility; work that is suspected of bias will not transcend the current atmosphere of distrust. We see advantages in placing the Board outside the government. In particular, the Board should be able to draw on the widest pool of scientific experts and not be restricted to government scientists; placement in the government might hinder the perception that the Board is free from the policy orientation of the administration in power; and direct involvement by the regulatory agencies themselves could detract from their ability to make regulatory decisions while the guidelines were in preparation.

The Committee has evaluated a number of possible organizational bases for the Board. The National Toxicology Program has had relevant experience with the scientific basis of risk assessment, but it already has major responsibility for coordinating testing of chemicals of interest to regulatory agencies. The Congressional Office of Technology Assessment is another possibility. However, the governance of the Office of Technology Assessment by a board composed of members of Congress could prove a practical impediment to the production of guidelines. Guidelines would clearly have policy ramifications that may be at variance with the established policy positions of OTA board members. The Office of Science and Technology Policy or the Office of Management and Budget could provide government-wide coordination; both are in the Executive Office of the President and are well positioned to ensure agency response and uniform implementation of guidelines and other Board findings. The major disadvantage of location in the Executive Office of the President is the lack of independence and, consequently, the greater likelihood of mixing scientific and policy considerations. All these organizations share the major drawback that they are in the government.

A special-purpose national (or Presidential) commission on risk assessment methods could attract eminent scientists to service and could be designed to balance viewpoints, but would lack permanence and policy experience. Professional societies constitute another class of possible candidates, but they generally have limited familiarity with policy studies.

We conclude that the National Academy of Sciences-National Research Council meets the four criteria for placement. The AIHC proposal addressed the same general concerns that have occupied this Committee and concluded that the most appropriate locus for the central panel was in the NAS-NRC. Although we do not concur in the idea of centralizing the performance of risk assessments, the arguments presented by the AIHC proposal for the selection of the NAS-NRC are fully applicable to the question of the placement of a Board that would address generic scientific issues in risk assessment. We believe that the Board could best function under NAS-NRC auspices, if the NAS-NRC agreed to provide them, and would be of great value in achieving many of the goals that we share with the authors of the AIHC proposal and of H.R. 638. Current NAS-NRC procedures for establishing, managing, and issuing study reports are appropriate for the prospective Board.

Qualifications of Members

We recommend that the Board consist of scientists with training and experience in the various disciplines involved in the process of risk assessment, including biostatistics, toxicology, epidemiology, environmental engineering, and clinical medicine. Other relevant fields—such as law, ethics, and the social sciences—should be included to ensure due appreciation of the policy context of Board activities. For the same reason, some members should have familiarity with regulatory programs. The nomination and selection of members should be in accordance with established NAS-NRC procedures. Service might be for staggered 3-year periods.

Sunset Review

The entire concept of the Board and its functions should be reviewed after approximately 6-8 years.

Appendix A

Background Information on Committee Members

REUEL A. STALLONES, Chairman, is Dean of the University of Texas School of Public Health in Houston. Dr. Stallones is an epidemiologist specializing in studies of risk factors in cardiovascular disease and is a member of the Institute of Medicine. He is a past member of the NRC Board on Toxicology and Environmental Health Hazards and has served on several NRC committees that evaluated the risks of environmental pollutants.

MORTON CORN is Director of the Division of Environmental Health Engineering at the School of Hygiene and Public Health, The Johns Hopkins University. He specializes in evaluation and engineering control of airborne chemical agents in the workplace and the atmosphere. Dr. Corn served as the Assistant Secretary of Labor for Occupational Safety and Health from October 1975 to January 1977. He is a member of the Panel of Experts in Occupational Health of the World Health Organization and serves on committees of EPA's Science Advisory Board and the Congressional Office of Technology Assessment.

KENNY S. CRUMP is President of Science Research Systems, Inc., a consulting firm specializing in the evaluation of statistical data and risk assessment. His work on methods of extrapolating from high to low doses is used by EPA's Carcinogen Assessment Group. He was previously with Louisiana Tech University where he was Professor of Mathematics and Statistics.

J. CLARENCE DAVIES is Executive Vice President of the Conservation Foundation. He has served on other NRC

committees dealing with regulatory issues, was chairman of the NRC Committee on Principles of Decision-Making for Regulating Chemicals in the Environment (1974-1975), and now serves on the Environmental Studies Board. Dr. Davies served for 6 years as a member of the Executive Committee of EPA's Science Advisory Board.

VINCENT P. DOLE is Professor of Medicine at Rockefeller University and conducts research on addictive behavior and metabolic diseases. Dr. Dole is a member of the National Academy of Sciences and has served as an NAS reviewer of a number of risk-related studies.

TED R. I. GREENWOOD is Associate Professor of Political Science at MIT. He has served as a Senior Policy Analyst in the Office of Science and Technology Policy (1977-1979). Dr. Greenwood has written about the problem of nuclear waste disposal and recently completed a monograph on the interaction between knowledge and discretion in regulatory decision-making.

RICHARD A. MERRILL is Dean of the Law School of the University of Virginia. He has been on the Law School faculty since 1969, except for 2 years (1975-1977), when he served as Chief Counsel to the FDA. He recently completed a study of regulatory decision-making on carcinogens for the Administrative Conference of the United States that focused on FDA's regulation of food contaminants, CPSC's regulation of chronic hazards, OSHA's program for workplace carcinogens, and the EPA pesticides program. Dean Merrill is a member of the Institute of Medicine and the NRC Board on Toxicology and Environmental Health Hazards. He teaches food and drug law, environmental health regulation, and administrative law.

FRANKLIN E. MIRER is Director of the Health and Safety Department of the International Union, United Auto Workers. Dr. Mirer, an industrial hygienist and toxicologist, has been with the UAW since 1975. He specializes in issues related to workplace chemical exposures and development of OSHA standards.

D. WARNER NORTH is a Principal with Decision Focus, Inc., a consulting firm specializing in decision analysis, and consulting Associate Professor with the Department

of Engineering-Economic Systems at Stanford University. Over the last 15 years, Dr. North has carried out applications of decision analysis and risk assessment to a variety of public-policy issues. He has participated in three previous NRC studies on air quality and toxic chemicals. His recent projects include work on methods for setting priorities and developing a regulatory strategy for toxic chemicals for the EPA Office of Toxic Substances. Dr. North has served on committees of the EPA Science Advisory Board since 1977.

GILBERT S. OMENN is Dean of the School of Public Health of the University of Washington in Seattle. A physician and geneticist, Dr. Omenn served in senior positions in the Office of Science and Technology Policy and in the Office of Management and Budget (1977-1981). He is a member of the Institute of Medicine. At OSTP, he was concerned with federal decision-making for public-health risks and was coauthor of a paper on the process for making such decisions. Before returning to the University of Washington, Dr. Omenn was a Fellow at the Brookings Institution, where he analyzed EPA's 1979 decision to revise the national ambient air quality standard for photochemical oxidants (measured as ozone).

JOSEPH V. RODRICKS is a Principal with ENVIRON Corporation, a Washington, D.C., consulting firm specializing in risks related to exposure to toxic substances. Dr. Rodricks, a biochemist, was with the FDA for 15 years (1965-1980). While at FDA, he served as Deputy Associate Commissioner and as chairman of an interagency work group on risk assessment that developed guidelines for member agencies to follow for determining risks associated with exposure to carcinogenic chemicals. Dr. Rodricks is a member of the NRC Board on Toxicology and Environmental Health Hazards and a Diplomate of the American Board of Toxicology.

PAUL SLOVIC is a psychologist at Decision Research in Eugene, Oregon. His research interests are related to human judgment in decision-making, with special emphasis on perception of risk, and he is coauthor of a book on the concept of acceptable risk. Dr. Slovic has served as a consultant to FDA, NSF, the National Institute of Mental Health, and the Nuclear Regulatory

Commission. He has been a council member of the Society for Risk Analysis and is President-elect of that organization.

H. MICHAEL D. UTIDJIAN is Corporate Medical Director at the American Cyanamid Company. Dr. Utidjian has been active in occupational medicine since 1961. Before gaining his current position, he was a Staff Scientist at Stanford Research Institute and served as a consultant to NIOSH. He also served as Associate Corporate Medical Director at Union Carbide.

ELIZABETH WEISBURGER is Assistant Director for Chemical Carcinogenesis at the National Cancer Institute. Dr. Weisburger, a toxicologist/oncologist, has been at NCI for 33 years and was involved in initial NCI decisions on establishing its bioassay program and determining which compounds to test.

Appendix B

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A. GUIDELINES AND POLICY FOR RISK ASSESSMENT

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Appendix C

Working Papers

(Photocopies of the collected working papers of the Committee on the Institutional Means for Assessment of Risks to Public Health are available from the National Academy Press, 2101 Constitution Avenue, NW, Washington, DC 20418)

CASE STUDY: CPSC'S RISK ASSESSMENT FOR FORMALDEHYDE

William M. Stigliani

CASE STUDY: NITRITE

Catherine L. St. Hilaire

CASE STUDY: ASBESTOS RISK ASSESSMENTS BY OSHA/NIOSH AND EPA

William M. Stigliani

AN ANATOMY OF RISK ASSESSMENT

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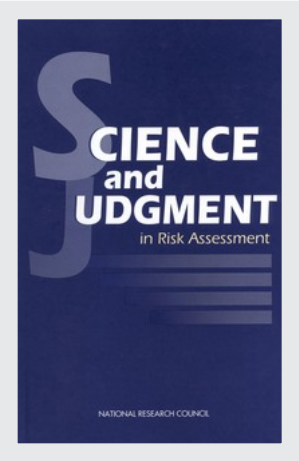
CURRENT FEDERAL PRACTICE IN RISK ASSESSMENT

Lawrence E. McCray and Robert I. Field



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Preface

In the Clean Air Act Amendments of 1990, Congress directed the administrator of the Environmental Protection Agency (EPA) to engage the National Academy of Sciences (NAS) in a review of the methods that EPA uses to estimates toxicological risk. The resulting charge to the National Research Council (NRC) can be summarized in a short set of questions:

1. Given that quantitative risk assessment is essential for EPA's implementation of the Clean Air Act, is EPA conducting risk assessments in the best possible manner?
2. Has EPA developed mechanisms for keeping its risk-assessment procedures current in the face of new developments in science?
3. Are adequate risk-related data being collected to permit EPA to carry out its mandates?
4. What, if anything, should be done to improve EPA's development and use of risk assessments?

To meet the congressional mandate, and in response to the request from the administrator of EPA, the National Research Council established the Committee on Risk Assessment of Hazardous Air Pollutants under the the Board on Environmental Studies and Toxicology. The committee consisted of 25 members with expertise in medicine, epidemiology, chemistry, chemical engineering, environmental health, law, pharmacology and toxicology, risk assessment, risk management, occupational health, statistics, air monitoring, and public health. It included academics, industry scientists, public advocates, and state and local public-health officials.

The first meeting of the committee was held on October 31, 1991. In the first several meetings, presentations were made to the committee by committee members and by individuals or representatives of groups with special concerns in the development and use of risk assessment. Among the latter were presenters on behalf of the American Industrial Health Council, the Chemical Manufacturers Association, the American Petroleum Institute, the American Iron and Steel Institute, the American Chemical Society, such official public-health groups as the Texas Air Control Board and the State and Territorial Air Pollution Program Administrators, and such public-interest groups as the Natural Resources Defense Council and the Environmental Defense Fund. Presentations were also made by the representative of a paint manufacturer and by a senior member of an environmental consulting company. The committee also was greatly aided by the previous reports and workshops of the NRC's Committee on Risk Assessment Methodology.

Early in the course of its deliberations the committee developed a set of issues for consideration and reply by EPA's Office of Air and Radiation and its Office of Research and Development. EPA's responses were presented to the committee during the committee's meetings in late March 1992.

James Powell, of the U.S. Senate staff, described to the committee both the legislative history of the Clean Air Act Amendments and the concerns of senators in the evolution of EPA's development of regulations. Greg Wetstone, of the U.S. House of Representatives staff, spoke to the committee about the need for accurate risk assessments and exposure measures. Henry Habicht, Michael Shapiro, Robert Kellum, and William Farland of EPA discussed where EPA was in risk assessment and how it got there. Their briefings enabled the committee to get off to a quick start in its work.

The committee was substantially helped in its activities by strong support from the NRC and BEST staff: Richard D. Thomas, the program director; Deborah D. Stine, the study director; Marvin A. Schneiderman, senior staff scientist; Norman Grossblatt, editor; Anne M. Sprague, information specialist; Ruth E. Crossgrove, information specialist; Ruth P. Danoff, project assistant; and Shelley A. Nurse and Catherine M. Kubik, senior project assistants.

Finally, we must express our thanks and appreciation to the hard-working members of the committee, who struggled through long meetings, read mountains of documents, listened with interest and concern to many presentations, and then prepared what we consider to be a thoughtful, comprehensive, and balanced report.

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Vice Chairman

Contents

Science and Judgment in Risk Assessment

Executive Summary

In recent decades, the public has become increasingly aware of seemingly innumerable reports of health threats from the environment. Myriad announcements about pesticides in food, pollutants in the air, chemical contaminants in drinking water, and hazardous-waste sites have created public concern about the chemical products and byproducts of modern industrial society. Alongside that concern is public skepticism about the reliability of scientific predictions concerning possible threats to human health. The skepticism has arisen in part because scientists disagree. But it is also apparent that many people want to understand the methods for assessing how much their exposures to chemicals threaten their health and well-being.

Many environmental issues that have risen to public prominence involve carcinogens—substances that can contribute to the development of cancer. Sometimes the decision that a substance is a carcinogen is based on evidence from workers exposed to high concentrations in the workplace, but more often it is based on evidence obtained in animals exposed to high concentrations in the laboratory. When such substances are found to occur in the general environment (even in much lower concentrations), efforts are made to determine the exposed population's risk of developing cancer, so that rational decisions can be made about the need for reducing exposure. However, scientists do not have and will not soon have reliable ways to measure carcinogenic risks to humans when exposures are small. In the absence of an ability to measure risk directly, they can offer only indirect and somewhat uncertain estimates.

Responses to these threats, often reflected in legislation and regulations, have led to reduced exposures to many pollutants. In recent years, however,

concerns have arisen that the threats posed by some regulated substances might have been overstated and, conversely, that some unregulated substances might pose greater threats than originally believed. Questions have also been raised about the economic costs of controlling or eliminating emissions of chemicals that might pose extremely small risks. Debates about reducing risks and controlling costs have been fed by the lack of universal agreement among scientists about which methods are best for assessing risk to humans.

Epidemiological studies—typically, comparisons of disease rates between exposed and unexposed populations—are not sufficiently precise to find that a substance poses a carcinogenic risk to humans except when the risk is very high or involves an unusual form of cancer. For this reason, animal studies generally provide the best means of assessing potential risks to humans. However, laboratory animals are usually exposed to toxicants at concentrations much higher than those experienced by humans in the general population. It is not usually known how similar the toxic responses in the test animals are to those in humans, and scientists do not have indisputable ways to measure or predict cancer risks associated with small exposures, such as those typically experienced by most people in the general environment.

Some hypotheses about carcinogens are qualitative. For example, biological data might suggest that any exposure to a carcinogen poses some health risk. Although some scientists disagree with that view or believe that it is not applicable to every carcinogen, its adoption provides at least a provisional answer to a vexing scientific question, namely whether people exposed to low concentrations of substances that are known to be carcinogenic at high concentrations are at *some* risk of cancer associated with the exposure. The view has dominated policy-making since the 1950s but is not always consistent with new scientific knowledge on the biological mechanisms of chemically induced cancer.

Beginning in the 1960s, toxicologists developed quantitative methods to estimate the risks associated with small exposures to carcinogens. If it were reliable, quantitative risk assessment could improve the ability of decision-makers and to some extent the public to discriminate between important and trivial threats and improve their ability to set priorities, evaluate tradeoffs among pollutants, and allocate public resources accordingly. In short, it could improve regulatory decisions that affect public health and the nation's economy.

During the 1970s and 1980s, methods of risk assessment continued to evolve, as did the underlying science. It became increasingly apparent that the process of carcinogenesis was complex, involving multiple steps and pathways. The concept that all cancer-causing chemicals act through mechanisms similar to those operative for radiation was challenged. Some chemicals were shown to alter DNA directly and hence to mimic radiation. But evidence developed that other chemicals cause cancer without directly altering or damaging DNA, for example, through hormonal pathways, by serving as mitogenic stimuli, or by causing excess cell death with compensatory cell proliferation. Biologically

based and pharmacokinetic models were introduced in some cases to describe exposure-response relationships more accurately. During the same period, substantial advances were made in modeling the dispersion of airborne materials from sources to receptors and in conducting exposure assessments. Furthermore, important advances have been made in the last 10 years in understanding the basic biology of chemical toxicity. All these advances are beginning to have a major impact on the estimation of risks associated with hazardous air pollutants.

REGULATION OF HAZARDOUS AIR POLLUTANTS

Before the enactment of the Clean Air Act Amendments of 1990 (1990 Amendments), Section 112 of the Clean Air Act required that the Environmental Protection Agency (EPA) set emission standards for hazardous air pollutants "to protect the public health with an ample margin of safety." In 1987, the District of Columbia Circuit Court of Appeals, in *Natural Resources Defense Council v. EPA* (824 F.2d 1146) interpreted this language to mean that EPA must first determine the emissions level that is safe—one that represents an acceptable degree of risk—and then add a margin of safety in light of the uncertainties in scientific knowledge about the pollutant in question. The agency was permitted to consider technological feasibility in the second step but not in the first.

In response, EPA decided that it would base its regulatory decisions largely on quantitative risk assessment. The agency adopted a general policy that a lifetime cancer risk of one in 10,000 for the most exposed person might constitute acceptable risk and that the margin of safety should reduce the risk for the greatest possible number of persons to an individual lifetime risk no higher than one in 1 million (10-6).

The 1990 Amendments rewrote Section 112 to place risk assessment in a key role but one secondary to technology-based regulation. As altered, Section 112 defines a list of substances as hazardous air pollutants, subject to addition or deletion by EPA. Sources that emit hazardous air pollutants will be regulated in two stages. In the first, technology-based emissions limits will be imposed. Each major source of hazardous air pollutants must meet an emission standard, to be issued by EPA, based on using the maximum achievable control technology (MACT). Smaller sources, known as area sources, must meet emissions standards based on using generally available control technology.

In the second stage, EPA must set "residual-risk standards that protect public health with an ample margin of safety if it concludes that the technology-based standards have not done so." The establishment of a residual-risk standard is required if the MACT emission standard leaves a lifetime cancer risk for the most exposed person of greater than one in a million. In actually setting the standard, though, EPA is free to continue to use its present policy of accepting higher risks. Quantitative risk assessment techniques will be relevant to this second stage of regulation, as well as to various decisions required in the first stage.

CHARGE TO THE STUDY COMMITTEE

Section 112(o) of the Act (quoted in full in Appendix M) directs the EPA to arrange for the National Academy of Sciences to:

- Review the methods used by EPA to determine the carcinogenic risk associated with exposure to hazardous air pollutant from sources subject to Section 112;
- Include in its review evaluations of the methods used for estimating the carcinogenic potency of hazardous air pollutants and for estimating human exposures to these air pollutants;
- Evaluate, to the extent practicable, risk-assessment methods for noncancer health effects for which safe thresholds might not exist.

The Academy's report must be considered by EPA in revising its present risk assessment guidelines.

CURRENT RISK-ASSESSMENT PRACTICES

Methods for estimating risk to humans exposed to toxicants have evolved steadily over the last few decades. Not until 1983, however, was the process codified in a formal way. In that year, the National Research Council released *Risk Assessment in the Federal Government: Managing the Process*. This publication, now known also as the Red Book, provided many of the definitions used throughout the environmental-health risk-assessment community today. The Red Book served as the basis for the general description of risk assessment used by the present committee.

Risk assessment entails the evaluation of information on the hazardous properties of substances, on the extent of human exposure to them, and on the characterization of the resulting risk. Risk assessment is not a single, fixed method of analysis. Rather, it is a systematic approach to organizing and analyzing scientific knowledge and information for potentially hazardous activities or for substances that might pose risks under specified conditions.

In brief, according to the Red Book, risk assessment can be divided into four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization.

- *Hazard identification* involves the determination of whether exposure to an agent can cause an increased incidence of an adverse health effect, such as cancer or birth defects, and characterization of the nature and strength of the evidence of causation.
- *Dose-response assessment* is the characterization of the relationship between exposure or dose and the incidence and severity of the adverse health effect. It includes consideration of factors that influence dose-response relationships, such as intensity and pattern of exposure and age and lifestyle variables

that could affect susceptibility. It can also involve extrapolation of high-dose responses to low-dose responses and from animal responses to human responses.

- *Exposure assessment* is the determination of the intensity, frequency, and duration of actual or hypothetical exposures of humans to the agent in question. In general, concentrations of the substance can be estimated at various points from its source through the environment. An important component of exposure assessment is emission characterization, i.e., determination of the magnitude and properties of the emissions that result in exposures. This is usually accomplished by measuring and analyzing emissions, but that is not always possible. Therefore, modeling is often used instead to establish the relationship between emissions and environmental concentrations of the substance. Inputs to such a model should include data on residence and activities of the exposed population.
- *Risk characterization* combines the assessments of exposure and response under various exposure conditions to estimate the probability of specific harm to an exposed individual or population. To the extent feasible, this characterization should include the distribution of risk in the population. When the distribution of risk is known, it is possible to estimate the risk to individuals who are most exposed to the substance in question.

Closely related to risk assessment is risk management, the process by which the results of risk assessment are integrated with other information—such as political, social, economic, and engineering considerations—to arrive at decisions about the need and methods for risk reduction. The authors of the Red Book advocated a clear conceptual distinction between risk assessment and risk management, noting, for instance, that maintaining the distinction between the two would help to prevent the tailoring of risk assessments to the political feasibility of regulating the substance in question. But they also recognized that the choice of risk-assessment techniques could not be isolated from society's risk-management goals. The result should be a process that supports the risk-management decisions required by the Clean Air Act and that provides appropriate incentives for further research to reduce important uncertainties on the extent of health risks.

In 1986, EPA issued risk-assessment guidelines that were generally consistent with the Red Book recommendations. The guidelines deal with assessing risks of carcinogenicity, mutagenicity, developmental toxicity, and effects of chemical mixtures. They include default options, which are essentially policy judgments of how to accommodate uncertainties. They include various assumptions that are needed for assessing exposure and risk, such as scaling factors to be used for converting test responses in rodents to estimated responses in humans.

As risk-assessment methods have evolved and been applied with increasing frequency in federal and state regulation of hazardous substances, regulated industries, environmental organizations, and academicians have leveled a broad

array of criticisms regarding the processes used by EPA. The concerns have included

- The lack of scientific data quantitatively relating chemical exposure to health risks.
- The divergence of opinion within the scientific community on the merits of the underlying scientific evidence.
- The lack of conformity among reported research results needed for risk characterization—e.g., the use of different methods for describing laboratory findings, which makes it difficult to compare the data from different laboratories and apply them in risk characterizations.
- The uncertainty of results produced by theoretical modeling, which is used in the absence of measurements.
- In response to its mandates, EPA has traditionally adopted risk assessments that for the most part incorporate conservative default options (i.e., those that are more likely to overstate than to understate human risk).
- As scientific knowledge increases, the science policy choices made by the agency and Congress should have less impact on regulatory decision-making. Better data and increased understanding of biological mechanisms should enable risk assessments that are less dependent on conservative default assumptions and more accurate as predictions of human risk.

STRATEGIES FOR RISK ASSESSMENT

The committee observed that several common themes cut across the various stages of risk assessment and arise in criticisms of each individual step. These themes are as follows:

- *Default options*. Is there a set of clear and consistent principles for modifying and departing from default options?
- *Data needs*. Is enough information available to EPA to generate risk assessments that are protective of public health and are scientifically plausible?
- *Validation*. Has the EPA made a sufficient case that its methods and models for carrying out risk assessments are consistent with current scientific information available?
- *Uncertainty*. Has EPA taken sufficient account of the need to consider, describe, and make decisions in light of the inevitable uncertainty in risk assessment?
- *Variability*. Has EPA sufficiently considered the extensive variation among individuals in their exposures to toxic substances and in their susceptibilities to cancer and other health effects?
- *Aggregation*. Is EPA appropriately addressing the possibility of interactions among pollutants in their effects on human health, and addressing the consideration of multiple exposure pathways and multiple adverse health effects?

By addressing each of those themes in each step in the risk-assessment process, EPA can improve the accuracy, precision, comprehensibility, and utility of the entire risk-assessment process in regulatory decision making.

Flexibility and the Use of Default Options

EPA's risk-assessment guidelines contain a number of "default options." These options are used in the absence of convincing scientific knowledge on which of several competing models and theories is correct. The options are not rules that bind the agency; rather, they constitute guidelines from which the agency may depart when evaluating the risks posed by a specific substance. For the most part, the defaults are conservative (i.e., they represent a choice that, although scientifically plausible given existing uncertainty, is more likely to result in overestimating than underestimating human risk).

EPA has acted reasonably in electing to formulate guidelines. EPA should have principles for choosing default options and for judging when and how to depart from them. Without such principles, the purposes of the default options could be undercut. The committee has identified a number of criteria that it believes ought to be taken into account in formulating such principles: protecting the public health, ensuring scientific validity, minimizing serious errors in estimating risks, maximizing incentives for research, creating an orderly and predictable process, and fostering openness and trustworthiness. There might be additional relevant criteria.

The choice of such principles goes beyond science and inevitably involves policy choices on how to balance such criteria. After extensive discussion, the committee found that it could not reach consensus on what the principles should be or on whether it was appropriate for this committee to recommend principles. Thus, the committee decided not to do so. Appendix N contains papers by several committee members containing varied perspectives on the appropriate choice of principles. Appendix N-1 advocates the principles of "plausible conservatism" and N-2 advocates the principle of the maximum use of scientific information in selection of default options. These papers do not purport to represent the views of all committee members.

The committee did agree, though, that EPA often does not clearly articulate in its risk-assessment guidelines that a specific assumption is a default option and that EPA does not fully explain in its guidelines the basis for each default option. Moreover, EPA has not stated all the default options in the risk-assessment process or acknowledged where defaults do not exist.

EPA's practice appears to be to allow departure from a default option in a specific case when it ascertains that there is a consensus among knowledgeable scientists that the available scientific evidence justifies departure from the default option. The agency relies on its Scientific Advisory Board and other expert bodies to determine when such a consensus exists. But EPA has not articulated criteria for allowing departures.

Recommendations

- EPA should continue to regard the use of default options as a reasonable way to deal with uncertainty about underlying mechanisms in selecting methods and models for use in risk assessment.
- EPA should explicitly identify each use of a default option in risk assessments.
- EPA should clearly state the scientific and policy basis for each default option.
- The agency should consider attempting to give greater formality to its criteria for a departure from default options, in order to give greater guidance to the public and to lessen the possibility of ad hoc, undocumented departures from default options that would undercut the scientific credibility of the agency's risk assessments. At the same time, the agency should be aware of the undesirability of having its guidelines evolve into inflexible rules.
- EPA should continue to use the Science Advisory Board and other expert bodies. In particular, the agency should continue to make the greatest possible use of peer review, workshops, and other devices to ensure broad peer and scientific participation to guarantee that its risk-assessment decisions will have access to the best science available through a process that allows full public discussion and peer participation by the scientific community.

Validation: Methods and Models

Some methods and models used in emission characterization, exposure assessment, hazard identification, and dose-response assessment are specified as default options. Others are sometimes used as alternatives to the default options. The predictive accuracy and uncertainty of these methods and models for risk assessment are not always clearly understood or clearly explained.

A threshold model (i.e., one that assumes that exposures below some level will not cause health effects) is generally accepted for reproductive and developmental toxicants, but it is not known how accurately it predicts human risk. The fact that current evidence on some toxicants, most notably lead, does not clearly reveal a safe threshold has raised concern that the threshold model might reflect the limits of scientific knowledge, rather than the limits of safety.

EPA has worked with outside groups to design studies to refine emission estimates. However, it does not have guidelines for the use of emission estimates in risk assessment, nor does it adequately evaluate the uncertainty in the estimates.

EPA has relied on Gaussian-plume models to estimate the concentrations of hazardous pollutants to which people are exposed. These representations of airborne transport processes are approximations. EPA focuses primarily on stationary outdoor emission sources of hazardous air pollutants. It does not have a

specific statutory mandate to consider all sources of hazardous air pollutants, but this should not deter the agency from assessing indoor sources to provide perspective in considering risks from outdoor sources.

EPA uses the Human-Exposure Model (HEM) to evaluate exposures from stationary sources. It estimates exposures and risk for both individuals and populations. For individuals, it has traditionally used a technique to determine what is called the maximally exposed individual (MEI) by estimating the highest exposure concentration that might be found among the broad distribution of possible exposures. Estimation of the maximum exposure is based on a variety of conservative assumptions, e.g., that the MEI lives directly downwind from the pollution source for his or her entire 70-year lifetime and remains outdoors the entire time. Traditionally, only exposure by inhalation is considered. Recently, in accordance with recommendations of the agency's Science Advisory Board, EPA has begun to replace the MEI estimate with two others: the high-end exposure estimate (HEEE) and the theoretical upper-bound exposure (TUBE).

In dose-response assessment, EPA has traditionally treated almost all chemical carcinogens as inducing cancer in a similar manner, mimicking radiation. It assumes that a linearized multistage model can be used to extrapolate from epidemiological observations (e.g., occupational studies) or experimental observations at high doses in laboratory animals down to the low doses usually experienced by humans in the general population.

Recommendations

- EPA should more rigorously establish the predictive accuracy and uncertainty of its methods and models and the quality of data used in risk assessment.
- EPA should develop guidelines for the amount and quality of emission information required for particular risk assessments and for estimating and reporting uncertainty in emission estimates, e.g., the predictive accuracy and uncertainty associated with each use of the HEM for exposure assessment.
- EPA should evaluate the Gaussian-plume models under realistic conditions of acceptable distances (based on population characteristics) to the site boundaries, complex terrain, poor plant dispersion characteristics, and the presence of other structures in the vicinity. Furthermore, EPA should consider incorporating such state-of-the-art techniques as stochastic-dispersion models.
- EPA should use a specific conservative mathematical technique to estimate the highest exposure likely to be encountered by an individual in the exposure group of interest.
- EPA should use bounding estimates for screening assessments to determine whether further levels of analysis are necessary. For further analyses, the committee supports EPA's development of distributions of exposures based on actual measurements, results from modeling, or both.
- EPA should continue to explore and, when scientifically appropriate, incorporate

pharmacokinetic models of the link between exposure and biologically effective dose (i.e., dose reaching the target tissue).

- EPA should continue to use the linearized multistage model as a default option but should develop criteria for determining when information is sufficient to use an alternative extrapolation model.
- EPA should develop biologically based quantitative methods for assessing the incidence and likelihood of noncancer effects in human populations resulting from chemical exposure. These methods should incorporate information on mechanisms of action and differences in susceptibility among populations and individuals that could affect risk.
- EPA should continue to use as one of its risk-characterization metrics, upper-bound potency estimates of the probability of developing cancer due to lifetime exposure. Whenever possible, this metric should be supplemented with other descriptions of cancer potency that might more adequately reflect the uncertainty associated with the estimates.

Priority-Setting and Data Needs

EPA does not have the exposure and toxicity data needed to establish the health risks associated with all 189 chemicals identified as hazardous air pollutants in the 1990 Amendments. Furthermore, EPA has not defined how it will determine the types, quantities, and quality of data that are needed to assess the risks posed by facilities that emit any of those 189 chemicals or how it will determine when site-specific emission and exposure data are needed.

Recommendations

- EPA should compile an inventory of the chemical, toxicological, clinical, and epidemiological literature on each of the 189 chemicals identified in the 1990 Amendments.
- EPA should screen the 189 chemicals to establish priorities according to procedures described by the committee for assessing health risks, identify data gaps, and develop incentives to expedite the generation of data by other government agencies (e.g., the National Toxicology Program, the Agency for Toxic Substances and Disease Registry, and state agencies), industry, and academe.
- In addition to stationary sources of hazardous air pollutants, EPA should consider mobile and indoor sources; the latter might be even more important than outdoor sources. The agency should also explicitly consider all direct and indirect routes of exposure, such as ingestion and dermal absorption.
- EPA should develop a two-part scheme for classifying evidence on carcinogenicity that would incorporate both a simple classification and a narrative evaluation. At a minimum, both parts should include the strength (quality) of the evidence, the relevance of the animal model and results to humans, and the

relevance of the experimental exposures (route, dose, timing, and duration) to those likely to be encountered by humans.

Variability

Many types of variability enter into the risk-assessment process: variability within individuals, among individuals, and among populations. Types of variability include nature and intensity of exposure and susceptibility to toxic insult related to age, lifestyle, genetic background, sex, ethnicity, and other factors.

Interindividual variability is not generally considered in EPA's cancer risk assessments. The agency's consideration of variability has been limited largely to noncarcinogenic effects, such as asthmatic responses to sulfur dioxide exposure. Analyses of such variability usually form the basis of decisions about whether to protect both the general population and sensitive individuals.

Recommendations

- Federal agencies should sponsor molecular, epidemiological, and other types of research to examine the causes and extent of interindividual variability in susceptibility to cancer and the possible correlations between susceptibility and such covariates as age, race, ethnicity, and sex. Results should be used to refine estimates of risks to individuals and the general population.
- EPA should adopt a default assumption for differences in susceptibility among humans in estimating individual risks.
- EPA should increase its efforts to validate or improve the default assumption that humans on average have the same susceptibility as humans in epidemiological studies, the most sensitive animals tested, or both.
- EPA's guidelines should clearly state a default assumption of nonthreshold, low-dose linearity for genetic effects on which adequate data might exist (e.g., data on chromosomal aberrations or dominant or X-linked mutations) so that a reasonable quantitative estimate of genetic risk to the first and later generations can be made for environmental chemical exposure.
- The distinction between uncertainty and individual variability should be maintained rigorously in each component of risk assessment.
- EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults.

Uncertainty

There are numerous gaps in scientific knowledge regarding hazardous air pollutants. Hence, there are many uncertainties in risk assessment. When the uncertainty concerns the magnitude of a quantity that can be measured or inferred from assumptions, such as exposure, the uncertainty can be quantified. Other uncertainties pertain to the models being used. These stem from a lack of

knowledge needed to determine which scientific theory is correct for a given chemical and population at risk and thus which assumptions should be used to derive estimates. Such uncertainties cannot be quantified on the basis of data.

The upperbound point estimate of risk typically computed by EPA does not convey the degree of uncertainty in the estimate. Thus, decision-makers do not know the extent of conservatism, if any, that is provided in the risk estimate.

Formal uncertainty analysis can help to inform EPA and the public about the extent of conservatism that is embedded in the default assumptions. Uncertainty analysis is especially useful in identifying where additional research is likely to resolve major uncertainties.

Uncertainty analysis should be an iterative process, moving from the identification of generic uncertainties to more refined analyses for chemical-specific or industrial plant-specific uncertainties. The additional resources needed to conduct the more specific analyses can be justified when the health or economic impacts of the regulatory decision are large and when further research is likely to change the decision.

Recommendations

- EPA should conduct formal uncertainty analyses, which can show where additional research might resolve major uncertainties and where it might not.
- EPA should consider in its risk assessments the limits of scientific knowledge, the remaining uncertainties, and the desire to identify errors of either overestimation or underestimation.
- EPA should develop guidelines for quantifying and communicating uncertainty (e.g., for models and data sets) as it occurs into each step in the risk-assessment process.
- Despite the advantages of developing consistent risk assessments between agencies by using common assumptions (e.g., replacing surface area with body weight to the 0.75 power), EPA should indicate other methods, if any, that might be more accurate.
- When ranking risks, EPA should consider the uncertainties in each estimate, rather than ranking solely on the basis of point estimate value. Risk managers should not be given only a single number or range of numbers. Rather, they should be given risk characterizations that are as robust (i.e., complete and accurate) as can be feasibly developed.

Aggregation

Typically, people at risk are exposed to a mixture of chemicals, each of which might be associated with an increased probability of one or more health effects. In such cases, data are often available on only one of the adverse effects

(e.g., cancer) associated with each chemical. At issue is how best to characterize and estimate the potential aggregate risk posed by exposure to a mixture of toxic chemicals. Furthermore, emitted substances might be carried to and deposited on other media, such as water and soil, and cause people to be exposed via routes other than inhalation, e.g., by dermal absorption or ingestion. EPA has not yet indicated whether it will consider multiple exposure routes for regulation under the 1990 Amendments, although it has done so in other regulatory contexts, e.g., under Superfund.

EPA adds the risks related to each chemical in a mixture in developing its risk estimate. This is generally considered appropriate when the only risk characterization needed is a point estimate for use in screening. When a more comprehensive uncertainty characterization is desired, EPA should adopt the following recommendations.

Recommendations

- EPA should consider using appropriate statistical (e.g., Monte Carlo) procedures to aggregate cancer risks from exposure to multiple compounds.
- In the analysis of animal bioassay data on the occurrence of multiple tumor types, the cancer potencies should be estimated for each relevant tumor type that is related to exposure, and the individual potencies should be summed for those tumors.
- Quantitative uncertainty characterizations conducted by EPA should appropriately reflect the difference between uncertainty and interindividual variability.

Communicating Risk

Certain expressions of probability are subjective, whether qualitative (e.g., that a threshold might exist) or quantitative (e.g., that there is a 90% probability that a threshold exists). Although quantitative probabilities could be useful in conveying the judgments of individual scientists to risk managers and to the public, the process of assessing probabilities is difficult. Because substantial disagreement and misunderstanding concerning the reliability of single numbers or even a range of numbers can occur, the basis for the numbers should be set forth clearly and in detail.

Recommendation

- Risk managers should be given characterizations of risk that are both qualitative and quantitative, i.e., both descriptive and mathematical.

An Iterative Approach

Resources and data are not sufficient to perform a full-scale risk assessment on each of the 189 chemicals listed as hazardous air pollutants in the 1990 Amendments, and in many cases no such assessment is needed. After MACT is applied, it is likely that some of the chemicals will pose only de minimis risk (a risk of adverse health effects of one in a million or less). For these reasons, the committee believes that EPA should undertake an iterative approach to risk assessment. An iterative approach would start with relatively inexpensive screening techniques—such as a simple, conservative transport model—and then for chemicals suspected of exceeding de minimis risk move on to more resource-intensive levels of data-gathering, model construction, and model application. To guard against serious underestimations of risk, screening techniques must err on the side of caution when there is uncertainty about model assumptions or parameter values.

Recommendations

- EPA should develop the ability to conduct iterative risk assessments that would allow improvements to be made in the estimates until (1) the risk is below the applicable decision-making level, (2) further improvements in the scientific knowledge would not significantly change the risk estimate, or (3) EPA, the emission source, or the public determines that the stakes are not high enough to warrant further analysis. Iterative risk assessments would also identify needs for further research and thus provide incentives for regulated parties to undertake research without the need for costly, case-by-case evaluations of each individual chemical. Iteration can improve the scientific basis of risk-assessment decisions while responding to risk-management concerns about such matters as the level of protection and resource constraints.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

The committee's findings are dominated by four central themes:

- Because of limitations on time, resources, scientific knowledge, and available data, EPA should generally retain its conservative, default-based approach to risk assessment for screening analysis in standard-setting; however, several corrective actions are needed to make this approach more effective.
- EPA should develop and use an iterative approach to risk assessment. This will lead to an improved understanding of the relationship between risk assessment and risk management and an appropriate blending of the two.
- The iterative approach proposed by the committee allows for improvements in the default-based approach by improving both models and the data used in analysis. For this approach to work properly, however, EPA needs to provide

justification for its current defaults and establish a procedure that permits departures from the default options.

- When EPA reports estimates of risk to decision-makers and the public, it should present not only point estimates of risk, but also the sources and magnitudes of uncertainty associated with these estimates.

Risk assessment is a set of tools, not an end in itself. The limited resources available should be spent to generate information that helps risk managers to choose the best possible course of action among the available options.

1

Introduction

In recent decades, there have been seemingly innumerable reports of health threats from the environment. Myriad announcements about pesticides in food, pollutants in the air, chemical contaminants in drinking water, and hazardous-waste sites have created public concern about the chemical products and byproducts of modern industrial society. Alongside that concern exists skepticism about many of the possible threats to human health. The skepticism has arisen in part because scientists disagree. But it is also apparent that most people want to understand whether and how much their exposures to chemicals threaten their health and well-being.

Many environmental issues that have risen to public prominence involve carcinogens—substances that can contribute to the development of cancer. Sometimes the decision that a substance is a carcinogen is based on evidence from workers exposed to high concentrations in the workplace, but more often it is based on evidence obtained in animals exposed to high concentrations in the laboratory. When such substances are found to occur in the general environment (even in much lower concentrations), efforts are made to determine the exposed population's risk of developing cancer, so that rational decisions can be made about the need for reducing exposure. However, scientists do not have and will not soon have reliable ways to measure carcinogenic risks when exposures are small. In the absence of an ability to measure risk directly, they can offer only indirect and somewhat uncertain estimates.

Some hypotheses about carcinogens are qualitative. For example, biological data suggests that any exposure to a carcinogen may pose some health risk. Although some scientists disagree with that view or believe that it is not applicable

to every carcinogen, its adoption provides at least a provisional answer to a vexing scientific question, namely whether people exposed to low concentrations of substances that are known to be carcinogenic at high concentrations are at *some* risk of cancer associated with the exposure. That view has been prominent since the 1950s and has guided much decision-making. For example, the "Delaney clause" of the Food Additive Amendments of 1958 stipulated that no additive that was found to be carcinogenic could be allowed in the food supply, on the grounds that it was not possible to specify a safe human exposure to such an agent. The policies that have flowed from regulations like the Delaney clause involve, where possible, absolute prohibition of exposures to carcinogens, but more commonly, reductions of exposures to the "lowest technically feasible level."

A qualitative response to the question of carcinogenic risk is still viewed by many scientists to be the best that can now be offered, even in the face of impressive scientific advances in understanding chemical carcinogenesis. Nonetheless, it is increasingly recognized that division of the binary division of the world of chemicals into carcinogens and non-carcinogens is overly simplistic and does not provide an adequate basis for regulatory decision-making. Beginning in the 1960s and coming to full force in the 1970s, some scientists have attempted to offer more useful, quantitative information about the risks of low exposures to carcinogens. Quantitative risk assessment is attractive because, at least ideally, it allows decision-makers and the public to discriminate between important and trivial threats (thus going beyond qualitative findings that there is some risk, however small).

The results of risk assessments are important in influencing important regulatory decisions that affect both the nation's economy and public health. They influence decision-makers as they attempt to balance the view that emission of hazardous air pollutants should be minimized or even eliminated, versus the view that meeting stringent control standards might cause other problems unacceptable to society. Accurate risk assessments are also needed to determine whether public health protection is adequate.

Charge To The Committee

The charge to the committee comes from Section 112(o) of the Clean Air Act, as added by the Clean Air Act Amendments of 1990, which requires EPA to enter into a contract with the National Research Council (NRC). NRC created the Committee on Risk Assessment of Hazardous Air Pollutants in the Board on Environmental Studies and Toxicology. Its charge is summarized as follows:

1. Review the risk assessment methods used by EPA (Environmental Protection Agency).

2. Evaluate methods used for estimating the carcinogenic potencies of hazardous air pollutants.
3. Evaluate methods used for estimating human exposures to hazardous air pollutants.
4. To the extent practicable, evaluate risk-assessment methods for noncancer health effects for which safe thresholds might not exist.
5. Indicate revisions needed in EPA's risk-assessment guidelines.

The specific congressional language is provided in Appendix M. Section 112(o) requires that if EPA decides not to comply with all of the report's recommendations and the Science Advisory Board's views of the report, it must provide a detailed explanation in the *Federal Register* of the reasons that any of the recommendations in the report are not implemented.

In its charge to EPA, Congress assigned NRC the task of evaluating whether EPA's risk-assessment methods express in a scientifically supportable way the risks posed by a substance. We therefore ask whether EPA's methods are consistent with current scientific knowledge. We also ask whether EPA's methods give policy-makers and the public the information they need to make judgments about risk management. Such methods should be logical and consistent and should, in particular, reveal the inevitable uncertainties in the underlying science.

We make no judgment regarding the appropriate risk-management decision, e.g., the extent to which society should control hazardous air pollutants. Such decisions ultimately hinge on nonscientific issues; for instance, the extent of risk from hazardous air pollutants that society is willing to accept in return for other benefits. Such issues involve not only science or science-policy judgments, but also matters of value on which scientists cannot purport to have any special insight. Such issues are therefore ultimately the province of policy-makers and the public.

It was precisely for this reason, we believe, that Congress specified in the Clean Air Act Amendments of 1990 that this committee is to undertake an investigation of EPA's risk-assessment methods, rather than of the validity of EPA's regulatory decisions. We have therefore refrained from addressing such risk management issues. We do, however, note that risk assessment and risk management are integrally related. As we explain later, Congress has generally directed EPA to be protective of health ("conservative" in the lexicon of public health) in its risk-management decisions. It is therefore essential for us to appraise whether EPA's risk-assessment methods are capable of supporting a policy of protective public-health regulation.

In addition, in its charge to EPA, Congress indicated that noncancer effects should be addressed to the extent feasible, but time constraints reduced the committee's ability to focus fully on this issue.

Section 303 of the 1990 Amendments created the Risk Assessment and Management Commission, part of whose charge is to examine risk-management policy issues. Specific subjects that the commission is to address are

- The report of the NRC committee.
- The use and limitations of risk assessment in establishing emission or effluent standards, ambient standards, exposure standards, acceptable concentrations, tolerances, or the environmental criteria for hazardous substances that present a risk of carcinogenic or other chronic health effects and the suitability of risk assessment for such purposes.
- The most appropriate methods for measuring and describing cancer risks or risks of other chronic health effects associated with exposure to hazardous substances.
- Methods to reflect uncertainties in measurement and estimation techniques, the existence of synergistic or antagonistic effects among hazardous substances, the accuracy of extrapolating animal-exposure data to human health risks, and the existence of unquantified direct or indirect effects on human health in risk-assessment studies.
- Risk-management policy issues, including the use of lifetime cancer risks to the people most exposed, the incidence of cancer, the cost and technical feasibility of exposure-reduction measures, and the use of site-specific actual exposure information in setting emission standards and other limitations applicable to sources of exposure to hazardous substances.
- The degree to which it is possible or desirable to develop a consistent risk-assessment method, or a consistent standard of acceptable risk among various federal programs.

Besides the Academy's report and the activities of the commission, both EPA and the Surgeon General are to evaluate the methods for evaluating health risks, the significance of residual risks, uncertainties associated with this analysis, and recommend legislative changes.

As a result, the committee highlights here some important and controversial subjects in risk assessment and management that it felt were beyond its charge.

1. *The use of a specific individual lifetime cancer risk number (e.g., 10^{-4} or 10^{-6})* as a target for risk regulations. The committee notes that Congress has set a standard for considering regulatory decisions. We note that such a number should be tied to a method and that uncertainty will always surround such estimates.
2. *The use of comparative risk analysis for the allocation of resources to minimize health impacts.* Congress decides how much of the country's economic and social resources should be spent on reducing threats to public health and how to allocate resources among the many threats present in our daily lives.
3. *The relative risk associated with synthetic or industrial byproducts versus*

natural chemicals. A recent study (Gold et al., 1992) contends that natural chemicals make up the vast bulk of chemicals to which humans are exposed, that natural chemicals are not much different from synthetic chemicals in their toxicology, and that about half the natural chemicals tested in chronic studies in rats and mice are carcinogens. The implication is that humans are likely to be exposed to a large background of rodent carcinogens as defined by high-dose testing. Some believe that this has implications for the amount of resources currently devoted to the study and control of synthetic chemicals. However, other studies (e.g., Perera and Bofetta, 1988) question the scientific underpinnings of these conclusions. The issue of the degree to which natural versus synthetic chemicals should be regulated is a policy issue that we cannot address. The scientific aspects of the issue will be discussed in a forthcoming NRC report on the relative risks of natural carcinogens. It is important to note that the present study focuses on airborne hazardous air pollutants and that, although some natural carcinogens are in food and water, there is little evidence of their widespread presence in air.

4. *The setting of relative policy priorities regarding the regulation of all sources of hazardous air pollutants.* The focus of Section 112 is on stationary sources of hazardous air pollutants; therefore, it was not within the charge of this committee to conduct an analysis of all sources of hazardous air pollutants and recommend which ones should be regulated and which should not. Congress already determined the extent to which it wanted to do that in the 1990 Amendments. Therefore, although the committee points out later in the report the potential impact of indoor versus outdoor pollutants, it is beyond our charge to go further and say whether, when, and how to take action on nonstationary and indoor sources of hazardous air pollutants.
5. *The uncertainty in engineering and economic assumptions.* There is, of course, uncertainty in the engineering and economic assumptions leading to EPA's estimates of the impact on industry of a regulation mandating specified magnitudes of risk. However, the committee was asked only to address EPA's implementation of risk assessment relative to public health, not the economic consequences of such regulation.
6. *The extent to which chemicals should be on or off the list of chemicals in the 1990 Amendments.* Although this report discusses how to set priorities for the collection and analysis of chemicals on the list, it is a policy judgment as to whether these chemicals, once ranked, should be included on such a list. (That does not imply that outside review of the list is not appropriate.)
7. *The presentation of uncertainty in the context of background risk.* Although this committee does discuss the issue of presentation of uncertainty, it was beyond its charge to indicate the extent to which it was appropriate to place the 1990 Amendments or other legislation in the context of all societal risk. Risk communication is complicated and involves such issues as involuntary versus voluntary risks, costs, benefits, and values, both individual and societal.

Conceptual Framework Of The Report

This report is aimed at a multidisciplinary audience with different levels of technical understanding. In discussing the many controversial aspects of risk assessment, the committee decided to address three categories of issues:

- Background of risk assessment and current practice at EPA. We organize this section (Chapters 2-5) via the old Red Book four-step paradigm.
- Specific concerns in risk assessment, such as the use of defaults and extrapolations. For example, is EPA justified in assuming, in the absence of contrary evidence, that the linearized multistage model should be used in determining the dose-response relationship for carcinogens?
- Cross-cutting issues that affect all parts of risk assessment. For example, how should uncertainty be handled? How should the accuracy of a model be evaluated?
- Implementation issues related to Section 112 of the 1990 Amendments. For example, how should EPA accommodate the tension between the goals of providing stability in its process and staying abreast of changing scientific knowledge?

The report addresses each type of issue. Our categorization of the issues reflects the analytical framework used by the committee and influences the structure of its recommendations. Although that might lead to some repetition, the committee feels that a degree of repetition is desirable because of the need to address audiences with different levels of knowledge.

The committee attempted to address the specific issues that arise from the uses of risk assessment under Section 112 of the Clean Air Act, which mandates the regulation of hazardous air pollutants. As amended in 1990, Section 112 deemphasizes risk assessment in the initial phase of regulation, in which EPA is to establish "technology-based" standards for categories of sources that emit hazardous air pollutants. Risk assessment's main role will be in the second phase of regulation, in which EPA must determine whether residual risk (the risk presented by the emissions remaining after compliance with technology-based standards) should be further reduced. Risk assessment will also be used in several other ways (e.g., to determine whether an entire source category may be exempted from technology-based standards on the grounds that no source in the category creates more than a one-in-a-million lifetime risk of cancer for the most exposed person).

The appendixes to the report include EPA's responses to questions from the committee and some important EPA documents not readily available. Risk assessment is an ever-changing process, and these documents illustrate its status within EPA during the time when the committee is making its recommendations.

Two documents were also prepared by some committee members to reflect the committee's inability to reach consensus on how EPA should choose and refine its "default options" for conducting risk assessments when basic scientific mechanisms are unknown. One view espouses a principle of "plausible conservatism," while the other advocates "making full use of science."

Part I

Current Approaches to Risk Assessment

The first part of the report examines the background and current practices of risk assessment consistent with the paradigm first codified in the 1983 NRC report *Risk Assessment in the Federal Government: Managing the Process*, often known as the Red Book (See Figure I-1). Chapter 2 of this report discusses the historical, social, and regulatory contexts of quantitative risk assessment. Chapters 3, 4, and 5 describe the Environmental Protection Agency's approach in applying the Red Book paradigm for risk assessment. As shown in Figure I-2, assessing human-health risks associated with a pollutant requires analysis of three elements: the *source* of the pollutant, the transport of the pollutant into the *environment* (air, water, land, and food), and the intake of the pollutant by *people* who might suffer adverse health effects either soon after exposure or later. Scientists and engineers take four basic interrelated steps to evaluate the potential health impact on people who are exposed to a hazardous air pollutant: emission characterization, exposure assessment, toxicity assessment, and risk characterization. In emission characterization, the chemical's identity and the magnitude of its emissions are determined. Exposure assessment includes how the pollutant moves from a source through the environment (transport) until it is converted to other substances (fate) or comes into contact with humans. In assessment of toxicity, the specific forms of toxicity that can be caused by the pollutant and the conditions under which these forms of toxicity might appear in exposed humans are evaluated. In risk characterization, the results of the analysis are described. These steps are described in detail in Chapters 3, 4, and 5.

The increase in the sophistication of the field of risk assessment since the Red Book requires risk assessors to have the ability to recognize and address fully such cross-cutting issues as uncertainty, variability, and aggregation, in

addition to having a more overarching view of the practice of risk assessment. Therefore, the committee supplements the Red Book paradigm with a second approach—one that is less fragmented (and hence more holistic), less linear and more interactive, and, most important, one organized not according to discipline or function, but according to the recurring conceptual issues that cut across all the stages of risk assessment. These cross-cutting issues are described in Part II of this report.

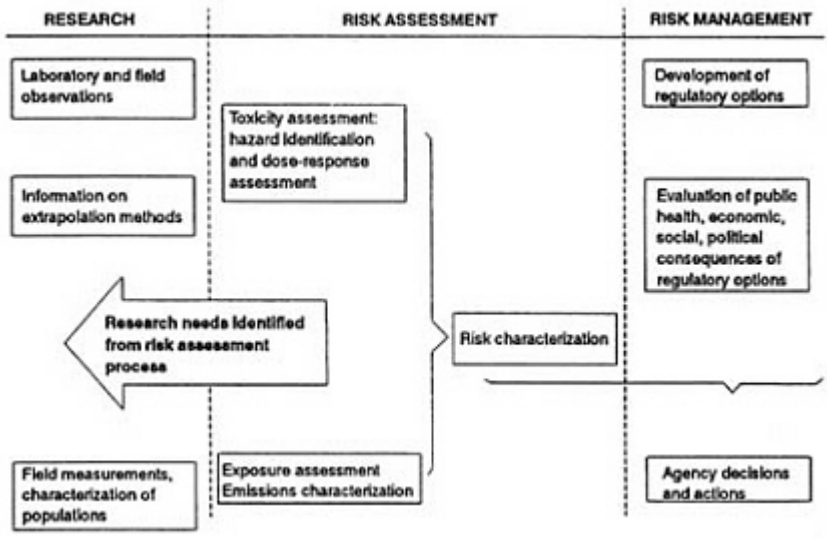


FIGURE I-1 NAS/NRC risk assessment/management paradigm. SOURCE: Adapted from NRC, 1983a.

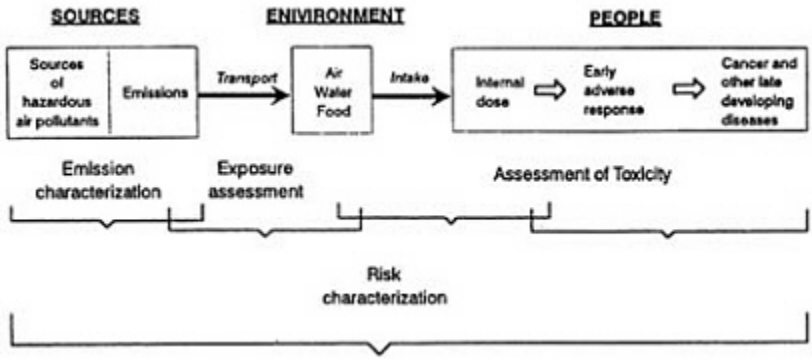


FIGURE I-2 Relationships in assessing human health risks of exposure to hazardous air pollutants. SOURCE: Adapted from NRC, 1983a.

2

Risk Assessment and Its Social and Regulatory Contexts

This chapter provides an overview of the origins and uses of quantitative risk assessment and the problems associated with it. Historical perspective is offered to aid understanding of how a method infused with so much uncertainty has still come to be seen by many as useful. Some attention is devoted to the important questions of how risk assessment has been used in decision-making and whether its use has improved decisions. The issues of public acceptance of the method and the degree to which decisions based on it are seen to provide adequate protection of the public health are also addressed. This chapter lists the major criticisms of risk assessment and the ways in which its results have been used, thus providing the justification for the selection of issues discussed in the succeeding chapters.

General Concepts

This section briefly discusses some basic definitions and concepts concerning human-health risk assessment, its content, and its relationships to research and to decision-making. The definitions and concepts were first systematically formulated by a National Research Council committee in a report issued in 1983, *Risk Assessment in the Federal Government: Managing the Process*. The Red Book had a major influence on the practice of risk assessment and will be discussed extensively in this section of the report.

What is Risk Assessment?

Human-health risk assessment entails the evaluation of scientific information on the hazardous properties of environmental agents and on the extent of

human exposure to those agents. The product of the evaluation is a statement regarding the probability that populations so exposed will be harmed, and to what degree. The probability may be expressed quantitatively or in relatively qualitative ways. There are other types of risk assessment that use similar processes but are outside the scope of this report, e.g., the risk assessment of the relative safety of a bridge.

Chemical hazards come in many forms. Some substances are radioactive, some explosive, some highly flammable. The particular hazard of concern here is chemical toxicity, including but not limited to carcinogenicity. Risk assessments can be carried out for any form of chemical toxicity. Risk assessment can be qualitative or quantitative. Many of the issues covered in this report concern quantitative expressions of risk.

How Is Risk Assessment Conducted?

The 1983 NRC report described a four-step analytic process for human-health risk assessment. A substance leaves a source (e.g., an industrial facility), moves through an environmental medium (e.g., the air), and results in an exposure (people breathe the air containing the chemical). The exposure creates a dose in the exposed people (the amount of the chemical entering the body, which may be expressed in any of several ways), and the magnitude, duration, and timing of the dose determine the extent to which the toxic properties of the chemical are realized in exposed people (the risk). This model is captured in the following analytic steps:

Step 1: **Hazard Identification** entails identification of the contaminants that are suspected to pose health hazards, quantification of the concentrations at which they are present in the environment, a description of the specific forms of toxicity (neurotoxicity, carcinogenicity, etc.) that can be caused by the contaminants of concern, and an evaluation of the conditions under which these forms of toxicity might be expressed in exposed humans. Information for this step is typically derived from environmental monitoring data and from epidemiologic and animal studies and other types of experimental work. This step is common to qualitative and quantitative risk assessment.

Step 2: **Dose-Response Assessment** entails a further evaluation of the conditions under which the toxic properties of a chemical might be manifested in exposed people, with particular emphasis on the quantitative relation between the dose and the toxic response. The development of this relationship may involve the use of mathematical models. This step may include an assessment of variations in response, for example, differences in susceptibility between young and old people.

Step 3: **Exposure Assessment** involves specifying the population that might be exposed to the agent of concern, identifying the routes through which

exposure can occur, and estimating the magnitude, duration, and timing of the doses that people might receive as a result of their exposure.

Step 4: **Risk Characterization** involves integration of information from the first three steps to develop a qualitative or quantitative estimate of the likelihood that any of the hazards associated with the agent of concern will be realized in exposed people. This is the step in which risk-assessment results are expressed. Risk characterization should also include a full discussion of the uncertainties associated with the estimates of risk.

Not every risk assessment encompasses all four steps. Risk assessment sometimes consists only of a hazard assessment designed to evaluate the potential of a substance to cause human health effects. Regulators sometimes take the additional step of ranking the potency of a number of chemicals—what is known as hazard ranking. Sometimes potency information is combined with exposure data to produce a risk ranking. These techniques all use some, but not all, of the four steps of the quantitative risk-assessment process.

Much of this report is devoted to the technical contents of the four steps of the process, because therein lie the issues that affect the reliability, utility, and credibility of risk-assessment outcomes. One important feature of those steps, however, needs to be emphasized here.

The 1983 NRC committee recognized that completion of the four steps rests on many judgments for which a scientific consensus has not been established. Risk assessors might be faced with several scientifically plausible approaches (e.g., choosing the most reliable dose-response model for extrapolation beyond the range of observable effects) with no definitive basis for distinguishing among them. The earlier committee pointed out that selection of a particular approach under such circumstances involves what it called a *science-policy* choice. Science-policy choices are distinct from the policy choices associated with ultimate decision-making, as will be seen below. The science-policy choices that regulatory agencies make in carrying out risk assessments have considerable influence on the results and are the focus of much that follows in this report.

What is the Relationship Between Risk Assessment and Research?

Although the conduct of a risk assessment involves research of a kind, it is primarily a process of gathering and evaluating extant data and imposing science-policy choices. Risk assessment draws on research in epidemiology, toxicology, statistics, pathology, molecular biology, biochemistry, analytical chemistry, exposure modeling, dosimetry, and other disciplines; to the extent that it attempts to capture and take into account uncertainties, it also draws on the research efforts of decision analysts.

Risk assessment, at least in theory, can influence research directions. Because, at its best, risk assessment provides a highly organized profile of the

current state of knowledge of particular issues and systematically elucidates scientific uncertainties, it can provide valuable guidance to research scientists regarding the types of data that can most effectively improve understanding. Little effort seems to have been made to use risk assessments in this way, although the Office of Technology Assessment has recently completed a study that describes the role of risk assessment in guiding research (OTA, 1993).

What is the Relationship Between Risk Assessment and Regulatory Decision-Making?

Risk management is the term used to describe the process by which risk-assessment results are integrated with other information to make decisions about the need for, method of, and extent of risk reduction. Policy considerations derived largely from statutory requirements dictate the extent to which risk information is used in decision-making and the extent to which other factors—such as technical feasibility, cost, and offsetting benefits—play a role.

Some statutes seem not to permit risk-assessment results to play a substantial role; they stress reductions of exposure to the "lowest technically feasible level" and usually require the best available technology. Proponents of such technology-based approaches often argue that they facilitate more rapid regulatory action and are especially suitable for making large and relatively inexpensive "first-cut" emission reductions. Proponents of quantitative risk assessment argue that such approaches are blind to the possibility that the risks remaining after application of such technology might still be unreasonably large or, in other situations, that they have been pushed to unnecessarily low values. As amended in 1990, Section 112 of the Clean Air Act gives quantitative risk-assessment results a secondary but still important role relative to technology-based controls.

What Is a Default Option?

EPA's guidelines set forth "default options." These are generic approaches, based on general scientific knowledge and policy judgment, that are applied to various elements of the risk assessment process when specific scientific information is not available. For instance, ambient doses of contaminants in humans are generally far lower than the doses that produce tumors in animals in controlled studies. The guidelines advise that, in assessing the magnitude of cancer risk to humans from low doses of a chemical based on the results of a high-dose experiment, "in the absence of adequate information to the contrary, the linearized multistage procedure will be employed" (EPA, 1986a, 1987a); that is, cancer risk in humans exposed to low doses will be estimated mathematically by using high-dose data and a curve-fitting procedure to extrapolate to low doses. Departure from the guideline is allowed if there is "adequate evidence" that the mechanism through which the substance is carcinogenic is more consistent with a

different model; for instance, that there is a threshold below which a substance will not cause a risk. Thus, the guideline amounts to a "default" that guides a decision-maker in the absence of evidence to the contrary; in effect, it assigns the burden of persuasion to those wishing to show that the linearized multistage procedure should not be used. Similar guidelines cover such important issues as the calculation of effective dose, the consideration of benign tumors, and the procedure for scaling animal-test results to estimates of potency in humans. In the absence of information on some critical point in a risk assessment, default procedures seem essential. The question, then, is not whether to use defaults, but which defaults are most appropriate for a specific task and when it is appropriate to use an alternative to a default.

Historical Roots

It is helpful to provide a brief historical perspective on the origins and evolution of risk assessment, so that some of the reasons that led to the use of the technique can be seen. The review is divided into two main parts, with an intervening section devoted to the NRC study of 1983 that was so influential in the developments of the last decade.

Early Efforts to Establish Safe Limits of Exposure to Toxic Substances

About 50 years ago, toxicologists began to study the problem of establishing limits on exposures to hazardous substances that would protect human health. The early efforts began in the 1940s in connection with concerns about occupational exposures to chemicals and about residues of pesticides in foods. Toxicologists were guided by the principle that all substances could become harmful under some conditions of exposure—when the so-called threshold dose was exceeded—but that human health could be protected as long as those exposure conditions were avoided. Threshold doses were recognized to vary widely among chemicals, but as long as human exposures were limited to subthreshold doses, no injury to health would be expected. The threshold hypothesis thus involved rejection of the simplistic view that the world is divided into toxic and nontoxic substances and acceptance of the principle that, for all chemicals, there were ranges of exposure that were toxic and ranges that were not. The threshold hypothesis was based on both empirical observations and basic concepts of biology—that every organism, including the human, has the capacity to adapt to or otherwise tolerate some exposure to any substance and that the harmful effects of a substance would become manifest only when exposure exceeded that capacity. Even at that early stage, there were questions about whether carcinogens always had thresholds, but otherwise the threshold concept became widely accepted.

Although there was widespread acceptance of the threshold hypothesis (except

among scientists working in genetics and in chemical carcinogenesis) (NRC, 1986), it was not apparent how the threshold dose was to be estimated for a large and diverse human population whose members have different thresholds of susceptibility. Experts in occupational health tended to rely heavily on observations of short-term toxicity in highly exposed workers and established acceptable exposure limits (the most prominent of which were the so-called threshold limit values, TLVs, first published by the American Conference of Governmental Industrial Hygienists in the 1950s) that were below the exposures that produced observable toxic effects. In the early 1950s, two Food and Drug Administration (FDA) scientists, O.G. Fitzhugh and A. Lehman, proposed a procedure for setting acceptable limits, which became known as acceptable daily intakes (ADIs), for dietary pesticide residues and food additives. Their procedure was based on the threshold hypothesis and first involved identification of a chemical's no-observed-effect level (NOEL) from the set of chronic animal-toxicity data in which the animals responded to the lowest dose tested—the "most sensitive" indication of the chemical's toxicity. Several response levels are characterized by acronyms. The first is the "no-observed-effect-level," NOEL. Earlier this was called the no-*observable*-effect level. *Observable* was changed to *observed* to be more in keeping with actual data ("observed"), rather than a rather vague potential "observable," which might be related to the size and sensitivity of the experiment. What is not observable in a small experiment might be easily observed in a large experiment. The word *adverse* was added to NOEL, making it NOAEL and making it clearer that *adverse* effects were of concern. The LOEL and LOAEL have a similar genesis and currently refer to the "lowest-observed-adverse-effect level"—the lowest dose at which an adverse effect was seen.

Fitzhugh and Lehman cited data suggesting that "average" human sensitivities might be up to 10 times those of laboratory animals and that some members of a large and diverse human population might be up to 10 times more sensitive than the "average" person. Thus came into use the safety factor of 100. The experimental NOEL was divided by 100 to arrive at a chemical-specific ADI. If human exposure was limited to daily amounts less than the ADI, then no toxicity was to be expected. In fact, Fitzhugh and Lehman, and later other authors and expert groups, including the World Health Organization, did not claim that an ADI arrived at in this fashion was risk-free, but only that it carried "reasonable certainty of no harm." No attempt was made to estimate the probability of harm. A variation of the safety-factor approach, often called margin of safety, is the estimate of the ratio of the NOEL to actual exposures. A judgment is made as to whether that ratio is acceptable. This margin-of-safety approach seems to be most common for substances already in general use, and in practice is often associated with lower ratios of NOEL to exposure than those based on safety factors.

The use of safety factors to establish ADIs was also recommended by various NRC committees (NRC, 1970, 1977, 1986) and adopted by the Joint Food

and Agriculture Organization and World Health Organization expert committees on food additives (FAO/WHO, 1982) and pesticide residues (FAO/WHO, 1965).

Although it has since been modified in several minor ways, the basic procedure for setting limits on human exposures to chemicals in air, water, and food persists to this day. The threshold hypothesis has been criticized as inadequate to account for some toxic effects, and it has not been accepted by regulators as applicable to carcinogens, but it remains a cornerstone of other regulatory and public-health risk assessments. Section 112 of EPA's authority for regulating toxic air pollutants envisions a safety-factor approach for some kinds of risk assessment.

The Problem of Carcinogens

Not only is cancer a much-feared set of diseases, but public and scientific concerns about cancer-inducing chemicals in the environment have centered on the possibility that such substances might act through nonthreshold mechanisms; that is, that exposure to even one molecule of a carcinogen is associated with a small but non-zero increased risk of tumor induction. This possibility served as the basis for modern dose-response models, which were developed initially from observations of radiation-induced cancer. These models came into wide use and were promoted by the National Research Council's series of reports entitled *Biological Effects of Ionizing Radiation* and later incorporated into the regulatory decision-making of the Nuclear Regulatory Commission. Perhaps the earliest legislative acknowledgment of the possibility that chemical carcinogens might act in the same way came in the form of the "Delaney clause" of the Food Additive Amendments of 1958. Following the suggestions set forth by several FDA and National Cancer Institute (NCI) officials, Congress stipulated that no additive that concentrates in food during processing or is added to food during or after processing may be allowed in the food supply if it is found to be carcinogenic in animals. The basis for the Delaney clause was that it is not possible to specify a safe human exposure to a carcinogen in the same sense that a safe intake of a substance acting through threshold mechanisms could be identified.

Through the 1960s and into the early 1970s, toxicologists avoided the problem of identifying "acceptable" intakes of carcinogens. Where it was possible, regulators simply prohibited introduction of carcinogens into commerce. But where banning was difficult or even infeasible—for example, for environmental contaminants that were byproducts of manufacturing and energy production—choosing a maximal permissible human exposure, and acceptance of some risk. Limits were sometimes based on some concept of technical feasibility. The problem with such a criterion for setting limits was that it provided little confidence that human health was being adequately protected or, conversely, that risks were not being forced to unnecessarily low levels. In many cases, carcinogenic pollutants were simply ignored (NRC, 1983a).

Those approaches to the problem of regulatory exposure to environmental carcinogens became problematic in the face of two trends. First, government and industrial testing for carcinogenicity began to increase rapidly during the late 1960s; during the 1970s, regulators had to begin to deal with large numbers of newly identified carcinogens that were found among the many commercial products introduced after World War II. Second, analytic chemists became able to identify carcinogens in the environment at lower and lower concentrations. It became clear during the early to middle 1970s that a systematic approach to regulating carcinogens was needed.

Several authors had published methods for quantifying low-dose risks associated with chemical carcinogen exposure in the 1960s and 1970s, and regulatory agencies—FDA and EPA in particular—began adopting some of the methods in the middle 1970s. EPA, for example, estimated low-dose risks associated with several carcinogenic pesticides and relied in part on its assessments in actions to cancel or limit their registrations. FDA began using low-dose risk estimation to deal with so-called indirect food additives and some food contaminants that proved to be carcinogenic. The Occupational Safety and Health Administration (OSHA) at first rejected the use of risk quantification as it mounted a major effort during the late 1970s to regulate occupational carcinogens, because it believed that the statute under which it operated did not permit the use of risk assessment. But a Supreme Court decision regarding the agency's efforts to establish a permissible exposure limit for benzene caused OSHA to incorporate risk quantification (see below).

Those trends of the 1970s toward increasing the use of risk assessment in carcinogen regulation caused several regulatory agencies, working together as the Interagency Regulatory Liaison Group (IRLG), to develop and publicize a set of guidelines for the conduct of risk assessments (IRLG, 1979). The guidelines were said by the agencies to specify a common approach to risk assessment. No commitment was made by the agencies to use the methods for all possible carcinogens in all classes of regulated products, but, to the extent that an agency decided to use risk assessment, its approach would be that specified in the IRLG guidelines. The agencies also noted that the guidelines did not include an approach to what later came to be called risk management; such issues were said to remain the prerogative of the individual agencies.

The IRLG guidelines embodied several important scientific principles that originated in efforts of the WHO International Agency for Cancer Research (IARC) (IARC, 1972, 1982), NCI (Shubik, 1977), and the federal regulatory agencies 9FDA, 1971; Albert et al., 1977; OSHA, 1982). Among them were principles concerning the appropriate uses of epidemiologic and animal data in identifying potential human carcinogens and the extrapolation of such data to humans. The IRLG guidelines did not explicitly incorporate the "default options" language described earlier (that came only after the 1983 NRC report), but

it is clear that they do include science-policy choices (e.g., the generic adoption of a linearized, no-threshold model for carcinogen dose-response assessment).

By the early 1980s, risk assessment had begun to take on considerable importance within the regulatory agencies and to capture the attention of regulated industries. One important impetus to the development of risk-assessment techniques was the Supreme Court's decision in *Industrial Union Department, AFLCIO v. American Petroleum Institute* , 448 U.S. 607 (1980), the "*Benzene*" decision. That decision struck down the OSHA standard for exposure to benzene in the workplace. The standard was based on OSHA's policy of trying to reduce concentrations of carcinogens in the workplace as far as technological possible without consideration of whether existing concentrations posed a significant risk to health. There was no opinion for the majority of the Supreme Court in *Benzene*, but four justices concluded that, under the Occupational Safety and Health Act, OSHA could regulate only if it found that benzene posed a significant risk of harm. Although the plurality did not define *significant risk of harm* and stressed that the magnitude of the risk need not be determined precisely, the decision strongly signaled that some form of quantitative risk assessment was necessary as a prelude to deciding whether a risk was large enough to deserve regulation.

Under those circumstances, Congress instructed FDA to arrange for the National Research Council in 1981 to undertake a study of federal efforts to use risk assessment.

NRC Study Of Risk Assessment In The Federal Government

In 1983, NRC was asked to issue recommendations regarding the scientific basis of risk assessment and the institutional arrangements under which it was being conducted and used. In particular, NRC's charge involved a close examination of the possibility that risk assessment might be conducted by a separate, centralized scientific body that would serve all the relevant agencies. It was proposed that such an arrangement might reduce the influence of policy-makers on the conduct of risk assessment, so that there would be minimal opportunities for the results of risk assessments to be manipulated to meet predetermined policy objectives.

The NRC committee drew extensively on the earlier work of EPA, FDA, OSHA, IARC, and NCI, and much of its effort was directed at a synthesis of scientific principles and concepts first elucidated by these agencies. The NRC study did not, however, recommend specific methods for the conduct of risk assessment.

The risk assessment framework and specific definitions of risk assessment and its component steps from the 1983 NRC report have been widely adopted.

Many of the recommendations from the 1983 report have been implemented by EPA and other regulatory agencies. Two of the major recommendations of the committee, summarized below, are particularly relevant to this report:

- A clear conceptual distinction between risk assessment and risk management should be maintained. It is, however, not necessary—indeed, it is inadvisable—to provide for a physical separation of the two activities. (The committee rejected the proposal for the establishment of an independent scientific group that would perform risk assessments for the regulatory agencies.) Risk assessments should be undertaken with careful attention to the contexts in which those assessments will be used.
- Regulatory agencies should develop and use inference guidelines that detail the scientific basis for the conduct of risk assessment and that set forth the default options. The guidelines should be explicit about the steps of risk assessment that require such science-policy choices. The guidelines are necessary to avoid the appearance of case-by-case manipulation of assumptions to meet preset management goals. Guidelines should be flexible, however, and allow departures from defaults when data in specific cases show that a default option is not appropriate.

The NRC committee did not specify and particular methodologic approach to risk assessment, nor did it address the issue of which default options should be used by regulatory agencies. It did, however, note that provisions should be made for continuing review of the science underlying the guidelines and of the basis of the default options incorporated in them.

Events After Release Of The 1983 NRC Report

The Office of Science and Technology Policy (OSTP) brought together scientists from the regulatory agencies, the National Institutes of Health, and other federal agencies and, in 1985, issued a comprehensive review of the scientific basis of risk assessment of chemical carcinogens. The OSTP review adopted the framework for risk assessment proposed by the NRC committee and provided the individual regulatory agencies a basis for developing the type of guidelines recommended by that committee.

Alone among federal agencies, EPA adopted a set of guidelines for carcinogen risk assessment in 1986, as recommended by NRC. The EPA guidelines specify default options, note the distinction between risk assessment and risk management, and otherwise meet NRC's and OSTP's recommendations. EPA has issued guidelines for assessing risks associated with several other adverse health effects of toxic substances (without the benefit of OSTP review of the underlying science) and for the conduct of human exposure assessments. Beginning in 1984, it initiated work and published guidelines for evaluating mutagenicity,

developmental toxicity, effects of chemical mixtures, and human exposure (EPA, 1986a, 1987a). It later published proposed guidelines on female reproductive risk (EPA, 1988a), male reproductive risk (EPA, 1988b), and exposure-related measurements (EPA, 1988c). Final, revised guidelines on developmental toxicity were published in 1991 (EPA, 1991a). The agency is now in the process of issuing revised guidelines on cancer risk assessment and has issued revised guidelines for the assessment of human exposures (EPA, 1992a).

Increasing activity at the state level was first indicated by California's publication in 1985 of *Guidelines for Chemical Carcinogen Risk Assessments and Their Scientific Rationale* (CDHS, 1985). The purpose of the guidelines was "to clarify internal procedures which risk assessment staff of the California Department of Health Services will usually use to deal with certain decision points which are characteristic of most risk assessments." The authors went on to state why guidelines were thought necessary, in language consistent with earlier statements of IRLG (1979), NRC (1983a), OSTP (1985), and EPA (1987a):

> These California guidelines, while in harmony with recent federal statements on carcinogenic risk assessment, are more specific and practical. The Department of Health Services' staff believe that there are important advantages to the announcement of such flexible nonregulatory guidelines. First, the publishing of guidelines increases the likelihood of consistency in risk assessment among agencies and decreases the time spent repeatedly arguing risk assessment policy for each separate substance. Second, announcing guidelines in advance makes it clear that one is not tailoring risk assessment to justify some predetermined risk management decision. Third, specific guidelines allow the regulated community to predict what emissions, food residues, or other exposures are apt to be of public health concern. Fourth, the publication and discussion of these guidelines should make the process more understandable to risk managers who have to make decisions that depend in part on risk assessment determinations.

The NRC, OSTP, EPA, and California documents were produced during a time in which the uses of risk assessment to guide regulatory decision-making were expanding rapidly. Particularly important was EPA's adoption of risk assessment as a guide to decisions at Superfund and other hazardous-waste sites, including those covered by the Resource Conservation and Recovery Act (RCRA).

The agency also extended the uses of risk assessment to decisions regarding pesticide residues in food, carcinogenic contaminants of drinking-water supplies, industrial emissions of carcinogens to surface waters, and industrial chemicals subject to regulation under the Toxic Substances Control Act (TSCA). Risk-management approaches varied according to the specific legal requirements applicable to the sources of carcinogen exposure, but the EPA guidelines were intended to ensure that the agency's approach to risk assessment was uniform across the various programs.

Uses Of Risk Assessment In The Regulation Of Hazardous Air Pollutants

Section 112 of the Clean Air Act, as originally adopted in the Clean Air Act Amendments of 1970, required EPA to set emissions standards for hazardous air pollutants so as to protect public health with an "ample margin of safety." EPA was slow in carrying out that mandate, listing only eight chemicals as hazardous air pollutants in 20 years.[1] Standards were issued for only seven (there was no standard for coke ovens), and the standards that were issued covered only some of the sources that emit these pollutants. One major reason was the ambiguity of "ample margin of safety." Many commentators long thought that that term barred EPA from considering costs; EPA might well have to set a standard of zero for any pollutant for which no threshold could be defined (i.e., virtually all carcinogens).

That interpretation of the act (originally developed well before 1987), however, was unanimously rejected by the District of Columbia Circuit court in *Natural Resources Defense Council v. EPA* (824 F.2d 1146 [en banc] [D.C.Cir. 1987]). At the same time, the Court of Appeals also rejected EPA's position that it could use technologic or economic feasibility as the primary basis for standard-setting under Section 112. Instead, the court held that EPA had first to determine what concentration was "safe"—i.e., represented an acceptable degree of risk—and had then to select a margin of safety necessary to incorporate the uncertainties in scientific knowledge. In the latter step, but not the former, technological feasibility could be taken into account. In accordance with the plurality opinion in the Supreme Court's *Benzene* decision, the circuit court also held that EPA's standards did not have to eliminate all risk.

As in the *Benzene* case, the court did not define any particular method for EPA to use in determining what risks are acceptable. On remand, the agency, after taking comment on a number of possibilities, decided that it could not use any single metric as a measure of whether a risk is acceptable. Instead, it adopted a general presumption that a lifetime excess risk of cancer of approximately one in 10,000 (10^{-4}) for the most exposed person would constitute acceptable risk and that the margin of safety should reduce the risk for the greatest possible number of persons to an individual lifetime excess risk no higher than one in 1 million (10^{-6}). Such factors as incidence (e.g., the number of possible new cases of a disease in a population), the distribution of risks, and uncertainties would be taken into account in applying those benchmarks. The agency approach thus put primary emphasis on estimating individual lifetime risks through quantitative risk assessment.

Congress lessened the role of quantitative risk assessment for air-pollution regulation by rewriting Section 112 in Title III of the 1990 amendments. Congress defined 189 chemicals as hazardous (subject to possible deletion) and required technology-based controls on sources of those chemicals, as well as any

others that might be added to the list by EPA. Sources that emit hazardous air pollutants will be regulated in two stages. In the first, technology-based emissions standards will be imposed. Each major source (defined, generally, as a stationary source having the potential to emit 10 tons per year of a single hazardous air pollutant or 25 tons per year of a combination of hazardous air pollutants) must meet an emission standard based on using the maximum available control technology (MACT) as defined by standards to be issued by EPA. Smaller sources, known as area sources, must meet emissions standards based on using generally available control technology.

Section 112 defines some contexts in which quantitative risk assessment will remain important. First, quantitative risk assessment will be relevant in determining which categories of sources will not be subject to technology-based regulation; EPA may delete a source category from regulation if no source in the category poses a risk of greater than 10^{-6} to the "individual most exposed to emissions." Even here, judging from the use of the word "may," EPA is not required to make the deletion; thus, the results of the quantitative risk assessment need not be decisive.

Quantitative risk assessment has a greater, but still limited, role in the second stage of standard-setting under Section 112(f), the "residual-risk" stage. That section requires EPA to set standards that protect public health with an ample margin of safety if it concludes that the first stage of technology-based standard-setting has not done so. Second-stage standards must be set for a category of "major sources" if the first stage allows a residual risk of greater than 10^{-6} to the individual most exposed to emissions. This requirement might seem a wholesale adoption of risk management based on the maximally exposed person, but two points must be noted. First, the 10^{-6} criterion for standard-setting need only be an upper-limit screening device. EPA is free, if it chooses, to set second-stage standards for source categories posing lesser risks. Second, the actual second-stage standard need not be expressed in terms of quantitative risk. Section 112(f)(2) authorizes EPA to continue the $10^{-4}/10^{-6}$ approach described earlier, but it does not require the agency to do so. Instead, any methods is acceptable that comports with *NRDC v. EPA*'s requirement that the standards provide an "ample margin of safety" in addition to reducing risk to a level judged acceptable by EPA.

Such techniques as hazard assessment, hazard ranking, and risk ranking (discussed above), and in some cases quantitative risk assessment, can also play a role in the agency's decisions on questions such as these:

- *Should EPA modify the definition of "major source" to include sources emitting less than the statutory cutoffs?* Section 112(a) defines a major source as one with the potential to emit 10 tons per year of any single listed hazardous air pollutant or 25 tons of any combination of listed pollutants, but allows EPA to lower these thresholds for a pollutant on the basis of such factors as potency, persistence, and potential for bioaccumulation.

- *Should EPA list additional pollutants as hazardous or remove some pollutants from the list?* Section 112(b) establishes a list of 189 hazardous air pollutants and requires that EPA add a substance to the list on a determination, either on its own accord or in response to a petition, that the substance is "known to cause or may reasonably be anticipated to cause adverse effects to human health or adverse environmental effects." This standard represents a reaffirmation of the *Ethyl* decision (discussed later) that EPA may regulate in the face of scientific uncertainty about a substance's effects. EPA is required to delete a substance if it decides that data are adequate to show that the substance will not cause, or be reasonably anticipated to cause, an adverse effect. In deletions as well, the risks of uncertainty are put on the source.
- *Which sources of hazardous air pollutants ought EPA to regulate first?* Section 112 requires that EPA set technology-based standards for categories of major sources on a phased schedule beginning in 1992 and ending in 2000. In deciding the order in which standards will be set, EPA must consider known or expected adverse effects of the pollutants to be regulated, as well as the quantity and location of emissions, or reasonably anticipated emissions, of hazardous air pollutants in each category. EPA has completed this preliminary task (see EPA, 1992a).
- *What restrictions ought EPA to place on offsetting within plants?* Generally, a physical change at a plant that increases emissions of a hazardous air pollutant will subject the plant to special new-source requirements. Under Section 112(g), this will not be the case if the plant simultaneously decreases by an offsetting amount emissions of a more hazardous pollutant. Deciding which offsets, if any, qualify for Section 112(g) may require EPA to rank the relative potency of hazardous air pollutants.
- *What restrictions ought EPA to place on offsetting by sources seeking to qualify for the early-reduction program?* The "early-reduction" program will pose similar issues. Usually, a source will have up to 3 years to comply with an EPA standard for controlling hazardous air pollutants. A source can obtain a 6-year extension, however, if it shows that it has achieved by approximately the end of 1993 a reduction of at least 90% in emissions of hazardous air pollutants (95% for particulate hazardous air pollutants) from baseline emissions. EPA is required to disqualify reductions that were used to offset increases in emissions of pollutants for which high risks of adverse health effects might be associated with exposure even to small quantities. Here, too, EPA will have to grapple with the relative potency factors of hazardous air pollutants. These rules have already been issued (see EPA, 1992b).
- *Which substances should EPA attempt to control through its urban-area source program?* EPA is required to identify at least 30 hazardous air pollutants that, as the result of emissions from area sources (nonmajor sources other than vehicles or off-road engines), present the greatest threat to public health in the largest number of urban areas. The agency must also identify categories responsible

for those emissions and develop a national strategy that accounts for over 90% of the emissions of the identified air pollutants and that reduces by at least 75% the incidence of cancer attributed to exposure to hazardous air pollutants emitted by major and area sources.

- *Which pollutants ought EPA control under its authority to protect against accidental releases?* EPA must promulgate a list of 100 substances that, in the event of accidental release, are known to cause or can reasonably be expected to cause death, injury, or serious adverse effects to human health or the environment. The agency must also establish a "threshold quantity" for each. Operators of sources at which a listed substance is present in more than a threshold quantity must prepare a risk-management plan to prevent accidental releases.

Noncancer Risk Associated With Hazardous Air Pollutants

The current EPA approach to risk assessment for noncancer hazards posed by hazardous air pollutants, refined in several ways, is conceptually similar to the traditional approach to threshold agents described earlier. The agency identifies a so-called inhalation reference concentration (RfC). An RfC is defined by EPA as "an estimate (with uncertainty) of the concentration that is likely to be without appreciable risk of deleterious effects to the exposed population after continuous, lifetime exposure" (EPA, 1992b). RfCs are derived from chemical-specific toxicity data. The latter are used to identify the most sensitive indicator of a chemical's toxicity and the so-called no-observed-adverse-effect level (NOAEL) for that indicator effect. If the NOAEL is derived from an animal study, as is typically the case, it can be converted to a human equivalent concentration by taking into account species differences in respiratory physiology. Uncertainty factors, whose magnitudes depend on the nature of the toxic effect and the quantity and quality of the data on which the NOAEL is based, are applied to the human-equivalent NOAEL to estimate the RfC. That procedure is used for all forms of toxic hazard except carcinogenicity. The use of RfCs depends on the assumption that toxic effects will not occur until a threshold dose is exceeded (EPA, 1992b).

Another important provision of Title III of the 1990 Amendments was the requirement that environmental effects be included in the evaluation of a risk associated with a pollutant. An adverse environmental effect is defined in Section 112(a)(7) of the act as "any significant and widespread adverse effect, which may reasonably be anticipated, to wildlife, aquatic life, or other natural resources, including adverse impacts on populations of endangered species or significant degradation of environmental quality over broad areas." Appendix III of EPA's *Unfinished Business* report (EPA, 1987b) found that airborne toxic substances, toxic substances in surface waters, and pesticides and herbicides were in the second highest category of relative risk in the ecological and welfare categories.

Of particular concern in this report was the transport by air and water of toxic substances (heavy metals and organics) that accumulate in ecological food chains. Such bioaccumulation has impacts on both ecological resources and the use by humans of specific ecological populations (e.g., fish consumption). Ecological risk assessment is not discussed in this report except to the extent that bioaccumulation affects the health of people who eat and drink contaminated ecological resources, but is discussed in another recent NRC report entitled *Issues in Risk Assessment* (NRC, 1993a).

Public Criticism Of Conduct And Uses Of Risk Assessment

The development of risk-assessment methods and their expanding uses in the federal and state regulation of hazardous substances have been carefully scrutinized by interested parties in the regulated industries, environmental organizations, and academic institutions. That scrutiny has led to frequent and sharp criticisms of the methods used for assessing risk and of ways in which the results of risk assessment have been used to guide decision-making. The criticisms have not been directed solely at the use of risk assessment in regulation of hazardous air pollutants, but rather cover a range of uses.

We cite here some of the criticisms that have appeared in the literature or that have otherwise been presented to the committee, because they help to define the issues reviewed in this report. *We emphasize that our citation of these criticisms does not mean that we believe them to be valid. Nor is the order of their listing meant to suggest our opinion regarding their possible importance.*

Criticisms Pertaining to Conduct of Risk Assessment

(1) Some analysts have commented that the default options used by EPA (i.e., the science-policy components of risk assessment) are excessively "conservative" or are not consistent with current scientific knowledge. The cumulative and combined effect of the many conservative default options used by EPA might yield results that seriously overstate actual risks, and thus tend to overcontrol emissions.

(2) Some experts have noted that important aspects of risk are neglected by EPA. The agency does not appear to recognize the possibility of synergistic interactions when multiple chemical exposures occur, nor does it seem concerned that available data show extreme variability among individuals in their responses to toxic substances. The failure to deal with those issues can lead to serious underestimation of human risk, especially at very low exposures. A related issue is the overlooked problem of risk aggregation—how risks associated with multiple chemicals are to be combined.

(3) The default options used by EPA have, according to some, become excessively

rigid. The barriers to using alternative assumptions by incorporating chemical-specific data are said to be in effect impassable, because the degree of scientific certainty has never been explicitly or implicitly defined by EPA. The too-rigid adherence to the preselected default options also impedes research, because there is little likelihood that novel data will be incorporated into EPA risk assessments.

(4) Many commentators have stated that insufficient attention has been paid to the issue of human exposure itself. In particular, EPA has not defined the terms of exposure assessment with sufficient clarity. How are populations and subpopulations of interest to be characterized? What is meant by such terms as "maximally exposed individual" and "reasonable maximal exposure"? How are multiple exposure pathways to be assessed in evaluating individual's total risk associated with a hazardous air pollutant?

(5) Some have noted that the uncertainties in the results of risk assessments are inadequately described. Risks are most often reported as "point estimates," single numbers that admit to no uncertainty. Large uncertainties are often overlooked, and descriptions of risk as "upper bounds" are misleading and simplistic.

(6) According to some, insufficient attention has been devoted to noncancer risks. The NOEL-safety factor approach, although useful, is not scientifically rigorous.

(7) Some believe that we do not have sufficient knowledge to make risk estimates. In addition, some believe that a risk assessor can make risk calculations come out high or low, depending on what answer is desired. Thus, some people believe that credible risk assessment might be impossible to obtain with the existing state of science and risk-assessment institutions.

Criticisms Pertaining to the Relationship Between Risk Assessment and Risk Management

(1) Several commentators have concluded that the conceptual separation of risk assessment and risk management called for in the 1983 NRC report has resulted in procedural separation to the detriment of the process. Some commentators have viewed the publication of toxicity values (cancer potency factors and reference doses) by one office of EPA for the use of other offices (those responsible for regulatory decision-making) as a prime example of undesirable separation.

(2) According to some analysts, upper-bound point estimates of risk, produced solely for screening or risk-ranking purposes, have too often been used inappropriately as a definitive basis for decision-making. Such use might be attractive to decision-makers, but it seriously distorts the intentions of risk assessors who produce the estimates. Managers need to consider scientific uncertainties more fully.

(3) Several commentators have expressed the view that risk assessment is

too resource-intensive and thus impedes action. Given the substantial uncertainties in the results of risk assessment, it seems inappropriate to devote so much effort to its conduct. Moreover, no good mechanisms exist to resolve controversies, so debates over the appropriateness of various risk-assessment outcomes can be endless.

(4) Some reviewers, particularly those with state governments, believe that more effort needs to be devoted to defining the uses to which a risk assessment is to be put before it is attempted. Such planning will help to deal with the problem of resource allocation, because the amount of effort needed for a risk assessment can be more appropriately matched to its ultimate uses.

(5) Some analysts have pointed out that the failure to pay sufficient attention to the results of risk assessment has resulted in misplaced priorities and regulatory actions that are driven by social forces, not by science. They note that the fact that risk assessment is imperfect does not justify the use of decision-making approaches that suffer from even greater imperfections.

(6) On the other hand, some commentators feel that risk assessment has been given too much weight, especially in light of its methodological limitations and inability to account for unquantifiable features of risk, such as voluntariness and fear.

(7) Some analysts also point out that far too little attention has been devoted to research to improve risk-assessment methods. It is unfair simply to criticize the methods without offering risk assessors the means to improve them.

Are any of those criticisms justified? If so, what responses can be made to them? Can improvements be made? If so, how will they affect the conduct of risk assessment and the use of risk-assessment results in regulatory decision-making? These and related issues are the primary focus of Chapters 6-12 of this report.

Note

1. The chemicals listed as hazardous air pollutants under the National Standards for Hazardous Air Pollutants (NESHAP) (with the date of public notice): asbestos (3/71); benzene (6/77); beryllium (3/71); coke-oven emissions (9/84); inorganic arsenic (6/80); mercury (3/71); radionuclides (12/79); and vinyl chloride (12/75).

3

Exposure Assessment

Introduction

Accurate information on human exposure to hazardous air pollutants emitted by various sources is crucial to assessing their potential health risks. This chapter describes methods used to assess exposure to hazardous air pollutants. Section 112 of the Clean Air Act Amendments of 1990 applies to major sources that either singly or in combination emit defined quantities of one or more of the 189 hazardous air pollutants. The sources to which the act applies emit pollutants both continuously and episodically, and the pollutants can move from air to water, soil, or food.

In the terminology of the Environmental Protection Agency (EPA) and Title III of the 1990 Amendments, a major source of pollution is considered to be

> any stationary source or group of stationary sources located within a contiguous area and under common control that emits or has the potential to emit considering controls, in the aggregate, 10 tons per year or more of any hazardous air pollutant or 25 tons per year of any combination of hazardous air pollutants. The [EPA] Administrator may establish a lesser quantity, or in the case of radionuclides different criteria, for a major source than that specified in the previous sentence, on the basis of the potency of the air pollutant, persistence, potential for bioaccumulation, other characteristics of the air pollutant, or other relevant factors.

A stationary source is "any building, structure, emission source, or installation which emits or may emit any air pollutant."

As part of determining the health threat of a pollution source to humans, EPA assesses how a pollutant moves from a source through the environment

until it makes contact with humans in its original form or after conversion to other substances. For most airborne substances, inhalation is assumed to be the primary route of entry into the body. There has recently been an extensive review of advances in assessing human exposure to airborne constituents (NRC, 1991a). That review attempted to define exposure carefully as a part of the overall continuum that leads to illness brought about by environmental contaminants. The definition of exposure as a part of this continuum has been incorporated into the 1992 revised guidelines for exposure assessment developed by EPA (1992a).

Human exposure to a contaminant is an event consisting of contact with a specific contaminant concentration at a boundary between a human and the environment (e.g., skin or lung) for a specified interval; total exposure is determined by the integrated product of concentration and time. The amount of a substance that is absorbed or deposited in the body of an exposed person in a given period is the administered dose. Calculating the dose from the exposure depends on a number of factors, including the mode of entry into the body. For substances that move into the body through an opening—such as the mouth or nose via breathing, eating, or drinking—the dose depends on the amount of the carrier medium that enters the body. For airborne substances, the potential dose is the product of breathing rate (volume of air inhaled per unit of time), exposure concentration, and fractional deposition of the substance throughout the respiratory tract. However, an inhalation exposure will not lead to a dose if none of the substance is absorbed through the lung or deposited on the surface of the lung or other sections of the respiratory tract.

A pollutant can also enter the body through the skin or other exposed tissues, such as the eyes. The substance is then directly absorbed from the carrier medium into the tissue, often at a rate that is different from the rate of absorption of the carrier. The pollutant uptake rate is the amount of the pollutant absorbed per unit of time, and the dose is the product of exposure concentration and uptake rate at that concentration. The NRC report on exposure assessment (NRC, 1991a) provides a scientific framework to identify routes of entry and degree of contact and indicates how exposure assessment integrates data on emitted pollutants with biological effects.

Exposure assessment involves numerous techniques to identify a pollutant, pollutant sources, environmental media of exposure, transport through each medium, chemical and physical transformations, routes of entry to the body, intensity and frequency of contact, and spatial and temporal concentration patterns of the pollutant. Mathematical models that can be used to describe the relationships among emissions, exposures, and doses are shown in Appendix C.

Exposure to a contaminant can be estimated in three ways. It can be evaluated directly by having a person wear a device that measures the concentration of a pollutant when it comes into contact with the body. Environmental monitoring is an indirect method of determining exposure, in which a chemical's concentration is measured in an environmental medium at a particular site, and the extent

to which a person is exposed to that medium is used to estimate exposure. Finally, exposure can be estimated from the chemical's actual dose to the body, if it manifests itself in some known way through a measurable internal indicator (biological marker), such as the concentration of the substance or its metabolite in a body tissue or excreted material (NRC, 1991a). This is a direct method of exposure estimation and, unlike the other two, accounts for the amount of contaminant absorbed by the body. Each of these methods provides an independent estimate of exposure; when it is possible to use more than one approach, comparison of results can be useful in validating exposure estimates.

EPA's air-pollution regulatory programs have relied primarily on mathematical models to predict the dispersion of emissions to air and the potential for human exposure under different emission-control scenarios (see Appendix C for a description of EPA's Human Exposure Model). Source-emission estimates and meteorologic data were used to calculate the expected long-term ambient concentrations at various distances and directions from the source. Census data were used to estimate the number and location of people living near the source. A high-exposure scenario was estimated for a person (e.g., maximally exposed individual, MEI) assumed to be living near the source and constantly exposed for 70 years to the highest estimated air-pollutant concentration. EPA does not modify exposure estimates by including mobility of the population, shielding due to indoor locations, or additional exposures from indoor or other community sources. EPA also used a modeling approach to estimate the exposure of the local population to an average concentration of pollutant emitted from a source (EPA, 1985a).

1992 Exposure-Assessment Guidelines

EPA has recently promulgated a new set of exposure-assessment guidelines to replace the previous (1986) version (EPA, 1992a). The approach in the new guidelines is very different from that in the previous version and generally follows many of the concepts of exposure assessment presented in the 1991 NRC report (NRC, 1991a). The guidelines explicitly consider the need to estimate the distribution of exposures of individuals and populations and discuss the need to incorporate uncertainty analysis into exposure assessment. This approach is consistent with the most recent NRC recommendations on exposure analysis (NRC, 1993e).

The guidelines discuss the roles of both analytic measurement and mathematical modeling in estimating concentrations and durations of exposure. They do not recommend specific models, but suggest that models match the objectives of the particular exposure assessment being conducted and that they have the accuracy needed to achieve those objectives. They also call for detailed explication of the choices and assumptions that often must be made in the face of incomplete data and insufficient resources.

Exposure Calculation and the Maximally Exposed Individual

EPA has traditionally characterized exposure according to two criteria: exposure of the total population and exposure of a specified, usually highly or maximally exposed individual. The MEI's exposure is estimated as the plausible upper bound of the distribution of individual exposures. The reason for finding the MEI, as well as population exposure, is to assess whether any individual exposure might occur above a particular threshold that, as a policy matter, is considered to be important. Because the MEI's exposure level is intended to represent a potential upper bound, its calculation has involved a variety of conservative assumptions. Among the more conservative, and more contentious, were that the MEI lived for 70 years at the location deemed by the dispersion model to receive the heaviest annual average concentration, that the person stayed there 24 hours/day, and that there is no difference between outdoor and indoor concentrations. In practice, it is straightforward to estimate the exposure of an immobile MEI with the air-quality models described below. However, estimating exposure for a more typical person requires much more information as to his or her activities during the assessment period. Usually, these activities include spending a majority of time inside (where pollutant concentrations can be attenuated) and time spent in travel away from the residence. The 70-year, 24-hour/day and no-indoor-attenuation assumptions are, in effect, bounding estimates. Some people do live in a small community for a whole lifetime. Some people do spend virtually their whole life at home. And for some pollutants, there is little attenuation of pollutant concentrations indoors. Nonetheless, the occurrence of these conditions is rare, and it is even rarer that all these are found together.

In the most recent exposure guidelines, EPA no longer uses the term MEI, noting the difficulty in estimating it and the variety of its uses. The MEI has been replaced with two other estimators of the upper end of the individual exposure distribution, a "high-end exposure estimate" (HEEE) and the theoretical upper-bounding estimate (TUBE). The HEEE is not specifically defined ("the Agency has not set policy on this matter" [EPA, 1992a]); rather, the new exposure guidelines discuss some of the issues and procedures that should be considered as part of the choice of the methods and criteria. The HEEE is "a plausible estimate of exposure of the individual exposure of those persons at the upper end of an exposure distribution." *High end* is stated conceptually as "above the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest exposure." As is implied by those statements, the new guidelines have adopted the use of individual exposure distributions, and the HEEE is a value in the upper tail of that distribution. The exact percentile for the HEEE that should be picked from the exposure distribution is not specified, but, according to EPA, should be chosen to be consistent with the population size in the particular application. The TUBE is a "bounding calculation that can easily be calculated and is designed to estimate exposure, dose, and

risk levels that are expected to exceed the levels experienced by all individuals in the actual distribution. The TUBE is calculated by assuming limits for all the variables used to calculate exposure and dose that, when combined, will result in mathematically highest exposure or dose. …" In addition, calculation of the TUBE includes using a limiting case for the exposure-dose and dose-response relationships in calculating risk.

To be responsive to the concerns raised in the NRC (1991a) report, EPA changed its approach to the MEI. The TUBE is to be used only for bounding purposes and is to be superseded by the HEEE in detailed risk characterizations. Although the exposure guidelines are ambiguous in details about the determination of the HEEE, the HEEE is based on the estimation of the distribution of exposures that people might actually encounter. From the individual exposures, it is possible to develop population exposure (and risk) distributions and include uncertainty estimation, and personal-activity patterns. The details of these approaches are discussed in the applicable sections of this report (Chapters 10, 11, and 12).

The calculation of the exposure distribution for an individual requires knowledge of both the distribution of hazardous-pollutant concentrations and the distribution of times that the individual spends in places for which the concentrations are measured or modeled (time-activity patterns). For estimates of population exposure, the individual time-activity patterns are estimated for the population of the individuals that might be exposed.

Emission Characterization

The first step in exposure assessment is estimation of the quantity of toxic materials emitted by a given source. Emission characterization involves identifying the chemical components of emissions and determining the rates at which they are emitted. Although emission characterization is a necessary part of the exposure-assessment process, it is often conducted separately from exposure assessment to determine whether a given operation falls into one or another regulatory category.

Sources of Emissions

The emission rate often is considered to be proportional to the type and magnitude of industrial activity at a source. Emissions from a source might occur from process vents, handling equipment such as valves, pumps, etc., storage tanks, transfer, and wastewater collection and treatment. Process-vent emissions are released to the atmosphere from the use, consumption, reaction, and production of chemicals. Fugitive emissions are produced when chemicals "escape" from handling equipment, such as pumps and valves. Storage-tank emissions are released from the locations where chemical feedstocks or products are

stored. These emissions depend on the chemical properties of the product stored (e.g., the vapor pressure), the atmospheric conditions (e.g., temperature), the type of tank (e.g., fixed or floating roof), and the type of seal and venting used. Transfer emissions are produced as material is received from or loaded into storage tanks, tank trucks, rail cars, and marine vessels (e.g., barges and ships). When material is added to a storage tank, for example, it can displace contaminated air into the atmosphere. Wastewater collection and treatment emissions can be released into a plant's wastewater system when chemicals are processed and released from the wastewater treatment plant. In continuous processes, a malfunction (upset), startup, or shutdown of the process can result in a much greater emission than normal.

Emission Estimation Methods

EPA (1991c) has provided a detailed procedure for estimating the emissions from facilities that use hazardous chemicals. In estimating emissions, information is generally needed on the magnitude of use of given chemicals, the chemical characteristics of the chemicals, and the efficiency with which the emissions are controlled.

The EPA protocols (1991c) provide a tiered approach to emission estimations ranging from relatively simple emission factors to material balances and direct measurements. These approaches have varied accuracy in estimation and a wide range of costs.

An emission factor is a multiplication factor that allows determination of the average emissions likely to come from a facility on the basis of its level of activity (EPA, 1985b). Emission factors are calculated on the basis of average measured emissions at several facilities in a given industry (*Compilation of Air Pollutant Emission Factors* , commonly known as AP-42 [EPA, 1985b]).

A material balance is performed by assuming that the sum of the mass of chemical inputs minus the sum of the outputs, after all chemical changes and accumulation within the process or equipment have been accounted for, is the emission. In general, material balances produce information about emissions that depends on relatively small differences between the large numbers that characterize inputs (raw materials) and outputs (finished products, byproducts, and other wastes).

Emissions can be estimated with calculation methods presented in EPA (1988d) publications, such as *Protocols for Generating Unit-Specific Emission Estimates for Equipment Leaks of VOC and VHAP* (used for fugitive emissions). This emission-estimation method allows the development of site-specific emission factors based on testing a statistical number of sources at a facility. These site-specific emission factors can be used to develop emission estimates in the future.

Ideally, emissions from a source can be calculated on the basis of measured

concentrations of the pollutant in the source and the emission rate of the source. This approach can be very expensive and is not often used. The emission rates, characteristics of the source facility (stack height, plume temperature, etc.), and local topography (flat or complex terrain) are used to estimate the ambient concentrations of the hazardous pollutants to which people can be exposed.

Measurement Methods

The concentration of a given pollutant can be measured in each microenvironment. A microenvironment is a three-dimensional space with defined boundaries of which contaminant concentration is approximately spatially uniform during some specific period (Sexton and Ryan, 1988). There have been substantial improvements in analytic methods to measure concentrations, as described in a 1991 NRC report (NRC, 1991a). Modern methods in computerization of instruments, data recording, and data processing also permit much greater capability to obtain detailed information on the temporal and spatial variability of contaminants over a range of microenvironments. Other substantial improvements have enhanced the utility of personal monitors, which are worn by subjects directly and record the concentration or collect time-integrated samples of specific pollutants with which the wearers come into contact for specific intervals. For example, assessment of exposure to radiation has long made use of inexpensive, accurate, integrating dosimeters that were first developed when research on radioactive materials and the use of radioactivity were expanding rapidly. There are often substantial variations in the spatial distribution of radiation within a microenvironment, so individual dosimeters have been thought to provide the best estimates of individual exposure. Individual monitoring and extensive microenvironmental measurements are not generally practical for assessing exposures of the general population, but because of cost and the unwillingness of individuals to participate in exposure assessments, new instruments, including passive dosimeters for airborne chemicals, are likely to permit a similar strategy. These methods have been used in the TEAM studies (Wallace, 1987) to examine the total exposure of individuals to a number of volatile organic compounds in several locations around the country. This approach to exposure assessment has been applied in other research studies. One important finding of the TEAM studies (and others) is that substantially greater exposures to many contaminants occur indoors, both because of the higher concentrations and because most people spend considerably more time inside.

Although field measurement studies are generally expensive and require careful planning, organization, and quality-assurance programs, measurement programs can provide the large amounts of high-quality data needed to characterize environmental systems, to estimate exposure, and to develop, test, and evaluate models for evaluating exposure. Documented reliable models can then be used in place of more expensive, direct measurements. Reliable measurements

are generally needed to provide knowledge of emissions of chemicals that give rise to human exposures. However, measurements provide only information on the current status of the system. To allow for a broader range of meteorologic conditions, estimate the effects of changes in plant operating capabilities and procedures, or estimate the effects of an accident or upset condition, models are needed to estimate emissions and the transport of emitted materials in the atmosphere.

Modeling Used In Exposure Assessment

Mathematical models used in exposure assessment can be classified in two broad categories: models that predict exposure (in units of concentration multiplied by time) and models that predict concentration (in units of mass per volume). Exposure models can be used to estimate population exposures from small numbers of representative measurements. Although concentration (or air-quality) models are not truly exposure models, they can be combined with information on human time-activity patterns to estimate exposures.

Air-quality models are also used to predict the fate, such as deposition or chemical transformation, of atmospheric pollutants to which people can be exposed indirectly (e.g., through deposition of pollutants from air onto surface water followed by bioaccumulation in fish). Such models are central to risk assessment (see Figure 3-1). They constitute the only method of determining the total impact of diverse emissions on air quality and are key tools in assessing the impact of specific sources on future air-pollutant concentrations and deposition.

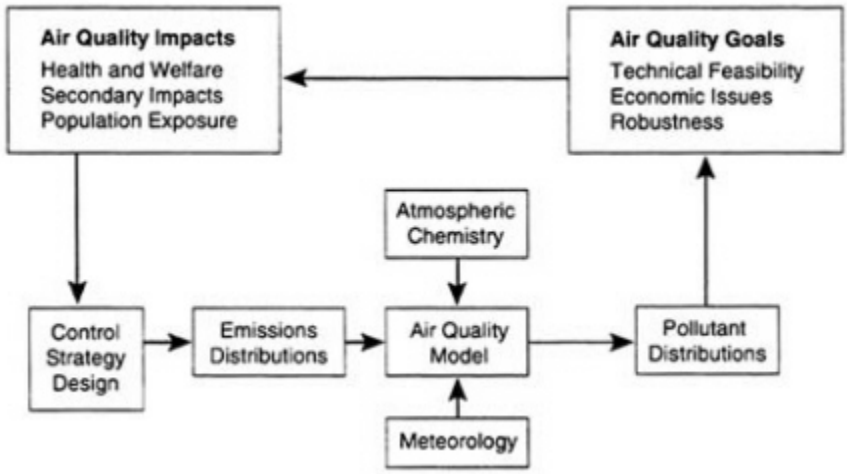


FIGURE 3-1 Air quality control strategy design process. SOURCE: Adapted from Russell et al., 1988.

Modeling Airborne Concentrations

Mathematical air-quality models used in air-pollution analysis are in two classes: empirical and analytic. The former type of model statistically relates observed air quality to the accompanying emission patterns, with chemistry and meteorology included only implicitly. Although they hold promise for use in some aspects of air-pollutant risk assessment, these models are not commonly used by EPA in its risk-assessment practice and will be discussed later. EPA and others more commonly use the form of analytical models, in which analytic or numerical expressions describe the complex transport processes and chemical reactions that affect air-pollutant concentrations. Pollutant concentrations are determined as explicit functions of meteorologic and topographic characteristics, chemical transformation, surface deposition, and source characteristics. In exposure assessments of air pollutants, the most widely used set of models has been the class called Gaussian-plume models. Gaussian-plume models are derived from atmospheric diffusion theory assuming stationary, homogeneous turbulence or, alternatively, by solution of the atmospheric-diffusion equation assuming simplified forms of the effective diffusivity (Seinfeld, 1986). Within the limits of the simplifications involved in their derivation, they can describe the individual processes that affect pollutant concentrations, such as diffusion, bulk transport by the wind, and deposition. These models are a type of a much broader family of models called dispersion or atmospheric-transport models. See Appendix C for more information.

Modeling Multimedia Exposure to Air Pollutants

In some cases, exposure to toxic pollutants emitted into the atmosphere occurs by pathways other than, or in addition to, inhalation. An example is deposition of metals like mercury in surface waters followed by the bioaccumulation of methyl mercury in fish and then ingestion of contaminated fish. Another is exposure of an infant ingesting the breast milk of a mother exposed to a toxic pollutant, such as polychlorinated biphenyls; this can be an important route for lipophilic compounds (NRC, 1993e), and EPA has investigated it in some exposure assessments. Recent studies (Travis and Hattemer-Frey, 1988; Bacci et al., 1990; Trapp et al., 1990) have also found significant bioaccumulation of chemicals from the atmosphere in plant tissues, particularly of nonionic organic compounds. These studies have found that the degree of bioaccumulation depends on solubility, and models for the uptake have been developed (Stevens, 1991). Such "indirect" pathways can concentrate pollutants and thus result in significant increases in exposure.

Multimedia exposure and indirect exposure have been considered more frequently in hazardous-waste site (e.g., Superfund) cleanup than in the management of exposure to industrial air pollutants. One example of multiple-path

exposure to a source of primary air pollutants conducted by EPA is found in Cleverly et al. (1992). Multiple air pollutants, including heavy metals and organic chemicals, were followed after emission from a municipal-waste combustor. Atmospheric transport and deposition were modeled with a Gaussian-plume model modified to include wet and dry deposition. Other models were used to assess pollutant concentrations in nearby bodies of water; bioaccumulation; consumption of animal tissue, plants, and water; soil ingestion; and total potential dose.

Alternative Transport and Fate Models

The 1992 EPA guidelines for exposure assessment offer an approach to selection and use of models to estimate transport and fate, as well as exposure, so a variety of models can be used. For rapid screening analyses, Gaussian-plume models are adequate for limited distances around the source. However, for a more complete characterization of the distribution of concentrations downwind of a source, more refined modeling approaches may be needed.

In recent years, stochastic modeling of atmospheric dispersion has increased in popularity because of its relatively simple concept, its applicability to more complicated problems, and the improvements in computer capability and costs that make such models practical. Stochastic models can easily incorporate real physical phenomena, such as buoyancy, droplet evaporation, variations in the dispersity of released particles, and dry deposition. Stochastic modeling is typically implemented as a numerical Monte Carlo model in which the movement of a large number of air parcels is tracked in a Lagrangian reference frame. The concentration profile is then obtained from the air-parcel positions.

Boughton et al. (1987) described a Monte Carlo simulation of atmospheric dispersion based on treating either parcel displacement or parcel velocity as a continuous-time Markov process (a one-step-memory random process like Brownian movement). They simplified the problem by restricting themselves to crosswind-integrated point sources and assumed that dispersion in the mean wind direction is negligible. Thus, they reduced the problem to a one-dimensional model. Liljegren (1989) extended the model to incorporate both horizontal and vertical dispersion perpendicular to the mean wind direction. He found good agreement between the results of the three-dimensional stochastic model with concentration data found in the literature. Recent measurements of the dispersion of ground-released smokes and obscurants have shown excellent agreement of his stochastic model both with the average concentration values, including the profile across the plume, and with the time-varying concentrations observed (pers. comm., W. E. Dunn, U. of Illinois, 1988). It appears from those results that stochastic models offer considerable improvement over conventional Gaussian-plume models. Thus, there will soon be a substantially improved ability to predict average and time-varying ground-level concentrations.

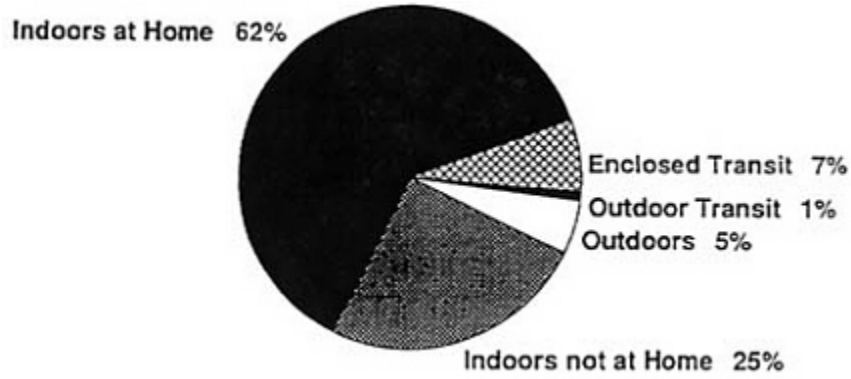


FIGURE 3-2 Percentage of day spent in different locations. Californians > 11 years of age. (Population Means). SOURCE: Jenkins et al., 1992. Reprinted with permission from *Atmospheric Environment*, copyright 1992 by Pergamon Press, Oxford, U.K.

Time-Activity Patterns

Exposure occurs when someone is in contact with a substance for some period. To estimate exposures, it is necessary to estimate the time spent in various activities that provide the opportunity for exposure. Figure 3-2 shows one such analysis. Various methods are available (NRC, 1991a), including recording of activities in a time-use diary (which might be automated to facilitate the recording of locations at specific times of the day and might use questionnaires to help reconstruct kinds and duration of activities). Some participants are careful in recording their activities; others might not provide accurate accounts, because of oversight or carelessness. The framing and wording of questionnaires can substantially affect the results of a survey and thus bias the resulting estimates of time spent in various activities and locations. Further work in the measurement and modeling of time and activity is needed; research recommendations were presented in an earlier report (NRC, 1991a).

Exposure-Assessment Models

The 1992 guidelines call for the development of distributions, instead of point estimates, for exposure parameters. It is the exposure-prediction models that combine microenvironmental concentration estimates with information on time-activity patterns of people to estimate individual exposures or the distribution of individual exposures in a typical population. Activity patterns and microenvironmental concentrations can both the measured or modeled. Microenvironmental concentrations and activity patterns can vary from person to person, and from period to period. Three types of models have been developed to estimate

population exposures: simulation models, such as the simulation of human air pollution exposure (SHAPE) model (Ott, 1981, 1984; Ott et al., 1988) and National Ambient Air Quality Standards (NAAQS) Exposure Model (NEM) (Johnson and Paul, 1981, 1983, 1984), the convolution model of Duan (1981, 1987), and the variance-components model of Duan (1988) and Switzer (1988) (see Appendix C for additional information). The development of total-exposure models is one of the advances in modeling.

Several of the models for predicting exposures assume some correlation between measured contaminant concentrations in a microenvironment and the time spent by the exposed person in that space. Studies by Duan et al. (1985) suggested, on the basis of data from the Washington, D.C., carbon monoxide (CO) study (Akland et al., 1985), that there is no correlation between CO concentrations and time. However, there will be problems in existing models if occupancy times and concentrations of other contaminants correlate, as they might for irritating toxicants, such as formaldehyde.

Current exposure models use a variety of crude assumptions about the constancy of concentrations in microenvironments, the human activity patterns that determine the amount of time people spend in each microenvironment, and how representative the sampled population is to the total population that might be exposed to a contaminant.

Long-Term Exposure Modeling

Modeling very-long-term exposures, as is required for cancer risk assessment, presents several major difficulties. The current practice is to measure or model the concentration of a contaminant at one time and determine lifetime exposure by multiplying that concentration by a fixed number of years, e.g., the lifetime of an exposed person. However, the nature of exposure sources (e.g., changes in industrial processes) and activity patterns can change substantially over a lifetime. New sources or uses of sources can be introduced into the environment (e.g., the spreading use of wood-burning stoves), and old sources can be eliminated or modified (e.g., by the use of catalytic converters in motor vehicles). Typically, large facilities have a design life of 30 years, so considerable change can be anticipated in sources over the 70 years of a typical lifetime-exposure calculation.

Time-activity patterns of people can also vary substantially over very long periods. In the United States, people generally change their place of residence frequently, although some live in the same place over a lifetime. Population mobility can have a large impact on exposure assessments of agents, such as radon, that require reasonable estimates of long-term and highly variable exposure concentrations.

A person's activity pattern changes from childhood through young adulthood to middle and old age. Some efforts have addressed age-related differences

in exposure that arise because of age. However, that aspect of variability in exposure over long periods has generally not received much attention in exposure modeling.

Short-Term Exposure Modeling

The typical steady-state airborne-concentration models are not able to provide estimates below 1-hour averages and have difficulty in modeling concentrations that vary widely over time and that can lead to short-term high exposures. If an exposure model is to estimate the effects of peak exposures on sensitive populations, the concentration model must provide reliable estimates for the time scales needed. There have been some important developments in stochastic models that could provide such estimates, but these developments have not yet been incorporated into the procedures for estimating exposure.

4

Assessment of Toxicity

Introduction

This chapter discusses the methods used to evaluate the toxicity of a substance for the purpose of health risk assessment. Evaluation of toxicity involves two steps: hazard identification and dose-response evaluation. Hazard identification includes a description of the specific forms of toxicity (neurotoxicity, carcinogenicity, etc.) that can be caused by a chemical and an evaluation of the conditions under which these forms of toxicity might appear in exposed humans. Data used in hazard identification typically are derived from animal studies and other types of experimental work, but can also come from epidemiologic studies. Dose-response evaluation is a more complex examination of the conditions under which the toxic properties of a chemical might be evidenced in exposed people, with particular emphasis on the quantitative relationship between dose and toxic response. This step also includes study of how response can vary from one population subgroup to another.

Principles Of Toxicity Assessment

The basic principles guiding the assessment of a substance's toxicity are outlined in the *Guidelines for Carcinogen Risk Assessment* (EPA, 1987a) (currently being updated), *Chemical Carcinogens: A Review of the Science and Its Associated Principles* (OSTP, 1985), *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991a) and have recently been summarized by the NRC (1993a). In addition, guidelines for the assessment of acute toxicity have recently been developed by NRC (1993b). The developmental-toxicity guidelines are

used in this chapter to illustrate EPA's approach to health effects that involve noncancer end points. They constitute the first completed noncancer risk-assessment guidelines in a series that EPA plans to issue.

Hazard Identification

The first of the two questions typically considered in the assessment of chemical toxicity concerns the types of toxic effects that the chemical can cause. Can it damage the liver, the kidney, the lung, or the reproductive system? Can it cause birth defects, neurotoxic effects, or cancer? This type of *hazard* information is obtained principally through studies in groups of people who happen to be exposed to the chemical (epidemiologic studies) and through controlled laboratory experiments involving various animal species. Several other types of experimental data can also be used to assist in identifying the toxic hazards of a chemical.

Epidemiologic Studies

Epidemiologic studies clearly provide the most relevant kind of information for hazard identification, simply because they involve observations of human beings, not laboratory animals. That obvious and substantial advantage is offset to various degrees by the difficulties associated with obtaining and interpreting epidemiologic information. It is often not possible to identify appropriate populations for study or to obtain the necessary medical information on the health status of individuals in them. Information on the magnitude and duration of chemical exposure, especially that experienced in the distant past, is often available in only qualitative or semiquantitative form (e.g., the number of years worked at low, medium, and high exposure). Identifying other factors that might influence the health status of a population is often not possible. Epidemiologic studies are not controlled experiments. The investigator identifies an exposure situation and attempts to identify appropriate "control" groups (i.e., unexposed parallel populations), but the ease with which this can be accomplished is largely beyond the investigator's control. For those and several other reasons, it is difficult or impossible to identify cause-effect relationships clearly with epidemiologic methods (OSTP, 1985).

It is rare that convincing causal relationships are identified with a single study. Epidemiologists usually weigh the results from several studies, ideally involving different populations and investigative methods, to determine whether there is a consistent pattern of responses among them. Some of the other factors that are often considered are the strength of the statistical association between a particular disease and exposure to the suspect chemical; whether the risk of the disease increases with increasing exposure to the suspect agent; and the degree to which other possible causative factors can be ruled out. Epidemiologists

attempt to reach consensus regarding causality by weighing the evidence. Needless to say, different experts will weigh such data differently, and consensus typically is not easily achieved (IARC, 1987).

In the case of chemicals suspected of causing cancer in humans, expert groups ("working groups") are regularly convened by the International Agency for Research on Cancer (IARC) to consider and evaluate epidemiologic evidence. These groups have published their conclusions regarding the "degrees" of strength of the evidence on specific chemicals (sometimes chemical mixtures or even industrial processes when individual causative agents cannot be identified). The highest degree of evidence—sufficient evidence of carcinogenicity—is applied only when a working group agrees that the total body of evidence is convincing with respect to the issue of a cause-effect relationship.

No similar consensus-building procedure has been established regarding other forms of toxicity. Some epidemiologists disagree with IARC's cancer classification judgments in particular cases, and there seems to be even greater potential for scientific controversy regarding the strength of the epidemiologic evidence of non-cancer (e.g., reproductive, developmental, etc.) effects. There has been much less epidemiologic study of other toxic effects, in part because of lack of adequate medical documentation.

Animal Studies

When epidemiologic studies are not available or not suitable, risk assessment may be based on studies of laboratory animals. One advantage of animal studies is that they can be controlled, so establishing causation (assuming that the experiments are well conducted) is not in general difficult. Another advantage is that animals can be used to collect toxicity information on chemicals before their marketing, whereas epidemiologic data can be collected only after human exposure. Indeed, laws in many countries require that some classes of chemicals (e.g., pesticides, food additives, and drugs) be subjected to toxicity testing in animals before marketing. Other advantages of animal tests include the facts that

- The quantitative relationship between exposure (or dose) and extent of toxic response can be established.
- The animals and animal tissues can be thoroughly examined by toxicologists and pathologists, so the full range of toxic effects produced by a chemical can be identified.
- The exposure duration and routes can be designed to match those experienced by the human population of concern.

But laboratory animals are not human beings, and this obvious fact is one clear disadvantage of animal studies. Another is the relatively high cost of animal studies containing enough animals to detect an effect of interest. Thus,

interpreting observations of toxicity in laboratory animals as generally applicable to humans usually requires two acts of extrapolation: interspecies extrapolation and extrapolation from high test doses to lower environmental doses. There are reasons based on both biologic principles and empirical observations to support the hypothesis that many forms of biologic responses, including toxic responses, can be extrapolated across mammalian species, including *Homo sapiens*, but the scientific basis of such extrapolation is not established with sufficient rigor to allow broad and definitive generalizations to be made (NRC, 1993b).

One of the most important reasons for species differences in response to chemical exposures is that toxicity is very often a function of chemical metabolism. Differences among animal species, or even among strains of the same species, in metabolic handling of a chemical, are not uncommon and can account for toxicity differences (NRC, 1986). Because in most cases information on a chemical's metabolic profile in humans is lacking (and often unobtainable), identifying the animal species and toxic response most likely to predict the human response accurately is generally not possible. It has become customary to assume, under these circumstances, that in the absence of clear evidence that a particular toxic response is not relevant to human beings, any observation of toxicity in an animal species is potentially predictive of response in at least some humans (EPA, 1987a). This is not unreasonable, given the great variation among humans in genetic composition, prior sensitizing events, and concurrent exposures to other agents.

As in the case of epidemiologic data, IARC expert panels rank evidence of carcinogenicity from animal studies. It is generally recognized by experts that evidence of carcinogenicity is most convincing when a chemical produces excess malignancies in several species and strains of laboratory animals and in both sexes. The observation that a much higher proportion of treated animals than untreated (control) animals develops malignancies adds weight to the evidence of carcinogenicity as a result of the exposure. At the other extreme, the observation that a chemical produces only a relatively small increase in incidence of mostly benign tumors, at a single site of the body, in a single species and sex of test animal does not make a very convincing case for carcinogenicity, although any excess of tumors raises some concern.

EPA combines human and animal evidence, as shown in Table 4-1, to categorize evidence of carcinogenicity; the agency's evaluations of data on individual carcinogens generally match those of IARC. For noncancer health effects, EPA uses categories like those outlined in Table 4-2. Animal data on other forms of toxicity are generally evaluated in the same way as carcinogenicity data, although this classification looks at hazard identification (qualitative) and dose-response relationships (quantitative) together. No risk or hazard ranking schemes similar to those used for carcinogens have been adopted.

The hazard-identification step of a risk assessment generally concludes with a qualitative narrative of the types of toxic responses, if any, that can be caused

TABLE 4-1 Categorization of Evidence of Carcinogenicity

Group		Criteria for Classification
A	Human carcinogen	Sufficient evidence from epidemiologic studies
B	Probable human carcinogen (two subgroups)	Limited evidence from epidemiologic studies and sufficient evidence from animal studies (B1); *or* inadequate evidence from epidemiologic studies (or no data) and sufficient evidence from animal studies (B2)
C	Possible human carcinogen	Limited evidence from animal studies and no human data
D	Not classifiable as to human carcinogenicity	Inadequate human and animal data or no data
E	Evidence of noncarcinogenicity in humans	No evidence of carcinogenicity from adequate human and animal studies

SOURCE: Adapted from EPA, 1987a.

by the chemical under review, the strength of the supporting evidence, and the scientific merits of the data and their value for predicting human toxicity. In addition to the epidemiologic and animal data, information on metabolism and on the behavior of the chemical in tissues and cells (i.e., on its mechanism of toxic action) might be evaluated, because clues to the reliability of interspecies extrapolation can often be found here.

Identifying the potential of a chemical to cause particular forms of toxicity in humans does not reveal whether the substance poses a risk in specific exposed populations. The latter determination requires three further analytic steps: emission characterization and exposure assessment (discussed in Chapter 3), dose-response assessment (discussed next), and risk characterization (discussed in Chapter 5).

Dose-Response Assessment

In the United States and many other countries, two forms of dose-response assessment involving extrapolation to low doses are used, depending on the nature of the toxic effect under consideration. One form is used for cancer, the other for toxic effects other than cancer.

Toxic Effects Other Than Cancer

For all types of toxic effects other than cancer, the standard procedure used by regulatory agencies for evaluating the dose-response aspects of toxicity involves identifying the highest exposure among all the available experimental

TABLE 4-2 Weight-of-Evidence Classification Methods for Noncancer Health Effects

Sufficient Evidence

The sufficient-evidence category includes data that collectively provide enough information to judge whether a human developmental hazard could exist within the context of dose, duration, timing, and route of exposure. This category includes both human and experimental-animal evidence.

Sufficient Human Evidence: This category includes data from epidemiologic studies (e.g., case-control and cohort studies) that provide convincing evidence for the scientific community to judge that a causal relationship is or is not supported. A case series in conjunction with strong supporting evidence may also be used. Supporting animal data might or might not be available.

Sufficient Experimental Animal Evidence or Limited Human Data: This category includes data from experimental-animal studies or limited human data that provide convincing evidence for the scientific community to judge whether the potential for developmental toxicity exists. The minimal evidence necessary to judge that a potential hazard exists generally would be data demonstrating an adverse developmental effect in a single appropriate, well-conducted study in a single experimental-animal species. The minimal evidence needed to judge that a potential hazard does not exist would include data from appropriate, well-conducted laboratory-animal studies in several species (at least two) that evaluated a variety of the potential manifestations of developmental toxicity and showed no developmental effects at doses that were minimally toxic to adults.

Insufficient Evidence

This category includes situations for which there is less than the minimal sufficient evidence necessary for assessing the potential for developmental toxicity, such as when no data are available on developmental toxicity, when the available data are from studies in animals or humans that have a limited design (e.g., small numbers, inappropriate dose selection or exposure information, or other uncontrolled factors), when the data are from a single species reported to have no adverse developmental effects, or when the data are limited to information on structure/activity relationships, short-term tests. pharmacokinetics, or metabolic precursors.

SOURCE: EPA, 1987a.

studies at which no toxic effect was observed, the "no-observed-effect level" (NOEL) or "no-observed-adverse-effect level" (NOAEL). The difference between the two values is related to the definition of adverse effect. The NOAEL is the highest exposure at which there is no statistically or biologically significant increase in the frequency of an adverse effect when compared with a control group. A similar value used is the lowest-observed-adverse-effect level (LOAEL), which is the lowest exposure at which there is a significant increase in an observable effect. All are used in a similar fashion relative to the regulatory need. The NOAEL is more conservative than the LOAEL (NRC, 1986).

For example, if a chemical caused signs of liver damage in rats at a dosage of 5 mg/kg per day, but no observable effect at 1 mg/kg per day and no other study indicated adverse effects at 1 mg/kg per day or less, then 5 mg/kg per day would be the LOAEL and 1 mg/kg per day would be the NOAEL under the conditions tested in that study. For human risk assessment, the ratio of the NOAEL to the estimated human dose gives an indication of the margin of safety for the potential risk. In general, the smaller the ratio, the greater the likelihood that some people will be adversely affected by the exposure.

The uncertainty-factor approach is used to set exposure limits for a chemical when there is reason to believe that a safe exposure exists; that is, that its toxic effects are likely to be expressed in a person only if that person's exposure is above some minimum, or threshold. At exposures below the threshold, toxic effects are unlikely. The experimental NOAEL is assumed to approximate the threshold. To establish limits for human exposure, the experimental NOAEL is divided by one or more uncertainty factors, which are intended to account for the uncertainty associated with interspecies and intraspecies extrapolation and other factors. Depending on how close the experimental threshold is thought to be to the exposure of a human population, perhaps modified by the particular conditions of exposure, a larger or smaller uncertainty factor might be required to ensure adequate protection. For example, if the NOAEL is derived from high-quality data in (necessarily limited groups of) humans, even a small safety factor (10 or less) might ensure safety, provided that the NOAEL was derived under conditions of exposure similar to those in the exposed population of interest and the study is otherwise sound. If, however, the NOAEL was derived from a less similar or less reliable laboratory-animal study, a larger uncertainty factor would be required (NRC, 1986).

There is no strong scientific basis for using the same constant uncertainty factor for all situations, but there are strong precedents for the use of some values (NRC, 1986). The regulatory agencies usually require values of 10,100, or 1,000 in different situations. For example, a factor of 100 is usually applied when the NOAEL is derived from chronic toxicity studies (typically 2-year studies) that are considered to be of high quality and when the purpose is to protect members of the general population who could be exposed daily for a full lifetime (10 to account for interspecies differences and 10 to account for intraspecies differences).

Using the NOAEL/LOAEL/uncertainty-factor procedure yields an estimate of an exposure that is thought to "have a reasonable certainty of no harm." Depending on the regulatory agency involved, the resulting estimate of "safe" exposure can be termed an acceptable daily intake, or ADI (Food and Drug Administration, FDA); a reference dose, or RfD (EPA); or a permissible exposure level, or PEL (Occupational Safety and Health Administration, OSHA). For risk assessments, the dose received by humans is compared with the ADI, RfD, or PEL to determine whether a health risk is likely.

The requirement for uncertainty factors stems in part from the belief that humans could be more sensitive to the toxic effects of a chemical than laboratory animals and the belief that variations in sensitivity are likely to exist within the human population (NRC, 1980a). Those beliefs are plausible, but the magnitudes of interspecies and intraspecies differences for every chemical and toxic end point are not often known. Uncertainty factors are intended to accommodate scientific uncertainty, as well as uncertainties about dose delivered, human variations in sensitivity, and other matters (Dourson and Stara, 1983).

EPA's approaches to risk assessment for chemically induced reproductive and developmental end points rely on the threshold assumption. The EPA (1987a) guidelines for health-risk assessment for suspected developmental toxicants states that, "owing primarily to a lack of understanding of the biological mechanisms underlying developmental toxicity, intra/interspecies differences in the types of developmental events, the influence of maternal effects on the dose-response curve, and whether or not a threshold exists below which no effect will be produced by an agent," many developmental toxicologists assume a threshold for most developmental effects, because "the embryo is known to have some capacity for repair of the damage or insult" and "most developmental deviations are probably multifactorial."

EPA (1988a,b) later proposed guidelines for assessing male and female reproductive risks that incorporate the threshold default assumption "usually assumed for noncarcinogenic/nonmutagenic health effects," as well as the agency's new RfD approach to deriving acceptable intakes. The RfD is obtained as described above. The total adjustment or uncertainty factor referred to in the proposed guidelines for use in obtaining an RfD from toxicity data "usually ranges" from 10 to 1,000. The adjustment incorporates (as needed) uncertainty factors ("often" 10) for "(1) situations in which the LOAEL must be used because a NOAEL was not established, (2) interspecies extrapolation, and (3) intraspecies adjustment for variable sensitivity among individuals." An additional modifying factor may be used to account for extrapolating between exposure durations (e.g., from acute to subchronic) or for NOAEL-LOAEL inadequacy due to scientific uncertainties in the available database.

EPA's 1992 revision of its guidelines for developmental-toxicity risk assessment state that "human data are preferred for risk assessment" and that the "most relevant information" is provided by good epidemiologic studies. When these data are not available, however, reproductive risk assessment and developmental-agent risk assessment, according to EPA, are based on four key assumptions:

- An agent that causes adverse developmental effects in animals will do so in humans, with sufficient exposure during development, although the types of effects might not be the same in humans as in animals.
- Any significant increase in any of the expressions of developmental toxicants

(e.g., death, structural abnormalities, growth alterations, and functional deficits) indicates a likelihood that the agent is a developmental hazard.

- Although the types of effects in humans and animals might not be the same, the use of the most sensitive animal species to estimate human hazards is justified.
- A threshold is assumed in dose-response relationships on the basis of current knowledge, although some experts believe that current science does not fully support this position.

The new guidelines state that "the existence of a NOAEL in an animal study does not prove or disprove the existence or level of a biological threshold." The guidelines also address statistical deficiencies and improvements in the NOAEL-based uncertainty-factor approach (Crump, 1984; Kimmel and Gaylor, 1988; Brown and Erdreich, 1989; Chen and Kodell, 1989; Gaylor, 1989; Kodell et al., 1991a). The guidelines also discuss EPA's plans to move toward a more quantitative "benchmark dose" (BD) for risk assessment for developmental end points "when sufficient data are available"; the BD approach would be consistent with the uncertainty-factor approach now in use (EPA, 1991a). Like the NOAEL and LOAEL, the BD is based on the most sensitive developmental effect observed in the most appropriate or most sensitive mammalian species. It would be derived by modeling the data in the observed range, selecting an incidence rate at a preset low observed response (e.g., 1% or 10%), and determining the corresponding lower confidence limit on dose that would yield that level of excess response. A BD thus calculated would then be divided by uncertainty factors to derive corresponding acceptable intake (e.g., RfD) values (EPA, 1991a). Thus, the traditional uncertainty-factor approach is retained in the 1991 developmental-toxicity guidelines, as well as in the proposed BD approach. However, the new guidelines are unique, in that they emphasize both the possible effect of interindividual variability in the interpretation of acceptable exposures and the improvements that biologically based models could bring to developmental risk assessment (EPA, 1991a):

> It has generally been assumed that there is a biological threshold for developmental toxicity; however, a threshold for a population of individuals may or may not exist because of other endogenous or exogenous factors that may increase the sensitivity of some individuals in the population. Thus, the addition of a toxicant may result in an increased risk for the population, but not necessarily for all individuals in the population. … Models that are biologically based should provide a more accurate estimation of low-dose risk to humans. … The Agency is currently supporting several major efforts to develop biologically based dose-response models for developmental toxicity risk assessment that include the consideration of threshold.

Cancer

For some toxic effects, notably cancer, there are reasons to believe either that no threshold for dose-response relationships exists or that, if one does exist, it is very low and cannot be reliably identified (OSTP, 1985; NRC, 1986). This approach is taken on the basis not of human experience with chemical-induced cancer, but rather of radiation-induced cancer in humans and radiologic theory of tissue damage. Risk estimation for carcinogens therefore follows a different procedure from that for noncarcinogens: the relationship between cancer incidence and the dose of a chemical observed in an epidemiologic or experimental study is extrapolated to the lower doses at which humans (e.g., neighboring population) might be exposed (e.g., due to emissions from a plant) to predict an excess lifetime risk of cancer—that is, the added risk of cancer resulting from lifetime exposure to that chemical at a particular dose. In this procedure, there is no "safe" dose with a risk of zero (except at zero dose), although at sufficiently low doses the risk becomes very low and is generally regarded as without publichealth significance.

The procedure used by EPA is typical of those used by the other regulatory agencies. The observed relationship between lifetime daily dose and observed tumor incidence is fitted to a mathematical model to predict the incidence at low doses. Several such models are in wide use. The so-called linearized multistage model (LMS) is favored by EPA for this purpose (EPA, 1987a). FDA uses a somewhat different procedure that nevertheless yields a similar result. An important feature of the LMS is that the dose-response curve is linear at low doses, even if it displays nonlinear behavior in the region of observation.

EPA applies a statistical confidence-limit procedure to the linear multistage no-threshold model to generate what is sometimes considered an upper bound on cancer risk. Although the actual risk cannot be known, it is thought that it will not exceed the upper bound, might be lower, and could be zero. The result of a dose-response assessment for a carcinogen is a potency factor. EPA also uses the term *unit risk factor* for cancer potency. This value is the plausible upper bound on excess lifetime risk of cancer per unit of dose. In the absence of strong evidence to the contrary, it is generally assumed that such a potency factor estimated from animal data can be applied to humans to estimate an upper bound on the human cancer risk associated with lifetime exposure to a specified dosage.

The dose-response step involves considerable uncertainty, because the shape of the dose-response curve at low doses is not derived from empirical observation, but must be inferred from theories that predict the shape of the curve at the low doses anticipated for human exposure. The adoption of linear models is based largely on the science-policy choice that calls for caution in the face of scientific uncertainty. Models that yield lower risks, indeed models incorporating a threshold dose, are plausible for many carcinogens, especially chemicals that do not directly interact with DNA and produce genetic alterations. For

example, some chemicals, such as chloroform, are thought to produce cancers in laboratory animals as a result of their cell-killing effects and related stimulation of cell division. However, in the absence of compelling mechanistic data to support such models, regulators are reluctant to use them, because of a fear that risk will be understated. For other substances (e.g., vinyl chloride), evidence shows that the human cancer risk at low doses could be substantially higher than would be estimated by the usual procedures from animal data. Models that yield higher potency estimates at lower doses than the LMS model might also be plausible, but are rarely used (Bailar et al., 1988).

New Trends In Toxicity Assessment

With respect to carcinogenic agents, two types of information are beginning to influence the conduct of risk assessment.

For any given chemical, a multitude of steps can occur between intake and the occurrence of adverse effects. Those events can occur dynamically over an extended period, in some cases decades. One approach to understanding the complex interrelationships is to divide the overall scheme into two pieces, the linkages between exposure and dose and between dose and response. *Pharmacokinetics* has often been used to describe the linkage between exposure (or intake) and dose, and *pharmacodynamics* to describe the linkage between dose and response. Use of the root *pharmaco* (for drug) reflects the origin of those terms. When applied to the study and evaluation of toxic materials, the corresponding terms might more appropriately be *toxicokinetics* and *toxicodynamics.*

Exploration of the use of pharmacokinetic data is especially vigorous. Risk assessors are seeking to understand the quantitative relationships between chemical exposures and target-site doses over a wide range of doses. Because the target-site dose is the ultimate determinant of risk, any nonlinearity in the relationship between administered dose and target-site dose or any quantitative differences in the ratio of the two quantities between humans and test animals could greatly influence the outcome of a risk assessment (which now generally relies on an assumed proportional relationship between administered and target doses). The problem of obtaining adequate pharmacokinetic data in humans is being attacked by the construction of physiologically based pharmacokinetic (PBPK) models, whose forms depend on the physiology of humans and test animals, solubilities of chemicals in various tissues, and relative rates of metabolism (NRC, 1989). Several relatively successful attempts at predicting tissue dose in humans and other species have been made with PBPK modeling, and greater uses of this tool are being encouraged by the regulatory community (NRC, 1987).

A second major trend in risk assessment stems from investigations indicating that some chemicals that increase tumor incidence might do so only indirectly, either by causing first cell-killing and then compensatory cell proliferation or by increasing rates of cell proliferation through mitogenesis. In either case,

increasing cell proliferation rates puts cells at increased risk of carcinogenesis from spontaneous mutation. Until a dose of such a carcinogen sufficient to cause the necessary toxicity or intracellular response is reached, no significant risk of cancer can exist. Such carcinogens, or their metabolites, show little or no propensity to damage genes (they are nongenotoxic).

5

Risk Characterization

Introduction

Characterization of risk is the final step in health risk assessment. This chapter discusses the methods used by the Environmental Protection Agency (EPA) to characterize the public-health risk associated with an emission source. In risk characterization, the assessor takes the exposure information from the exposure-assessment stage (discussed in Chapter 3) and combines it with information from the dose-response assessment stage (discussed in Chapter 4) to determine the likelihood that an emission could cause harm to nearby individuals and populations. The results of this risk characterization are then communicated to the risk manager with an overall assessment of the quality of the information in that analysis. The goal of risk characterization is to provide an understanding of the type and magnitude of an adverse effect that a particular chemical or emission could cause under particular circumstances. The risk manager then makes decisions on the basis of the public-health impact as determined by the risk characterization and other criteria outlined in the appropriate statute.

The elements of risk characterization are discussed here on the basis of several EPA documents, including EPA's *Risk Assessment Guidelines of 1986* (EPA, 1987a); *Guidelines for Exposure Assessment* (EPA, 1992a); a memorandum from Henry Habicht II, deputy administrator of EPA, dated February 26, 1992 (EPA, 1992c) (see Appendix B) (known hereafter as the "risk-characterization memorandum"); and *Risk Assessment Guidance for Superfund* (EPA, 1989a) (the "Superfund document").

Elements Of Risk Characterization

EPA's risk-characterization step has four elements: generation of a quantitative estimate of risk, qualitative description of uncertainty, presentation of the risk estimate, and communication of the results of risk analysis.

Quantitative Estimates of Risk

To determine the likelihood of an adverse effect in an exposed population, quantitative information on exposure—i.e., the dose (determined from the analysis in Chapter 3)—is combined with information on the dose-response relationship (determined from the analysis in Chapter 4). This process is different for carcinogens and for noncarcinogens. For noncarcinogens, the dose estimate is divided by the RfD to obtain a hazard index. If the hazard index is less than 1, the chemical exposure under consideration is regarded as unlikely to lead to adverse health effects. If the hazard index is greater than 1, adverse health effects are more likely and some remedial action is called for. The hazard index is thus not an actual measure of risk; it is a benchmark that can be used to estimate the likelihood of risk.

For carcinogens, excess lifetime risk is calculated by multiplying the dose estimate by a potency factor. The result is a value that represents an upper bound on the probability that lifetime exposure to an agent, under the specified conditions of exposure, will lead to excess cancer risk. This value is usually expressed as a population risk, such as 1×10^{-6}, which means that no more than one in 1 million exposed persons is expected to develop cancer. Risk estimates obtained in this way are *not* scientific estimates of actual cancer risk; they are upper bounds on actual cancer risk that are useful to regulators for setting priorities and for setting exposure limits.

When exposure to more than one agent occurs simultaneously, the cancer risk estimates obtained for each agent can be combined in an additive manner for each route of exposure. Hazard indexes for noncarcinogens may be combined when the agents of concern elicit similar end points of toxicity.

Sometimes, this risk-characterization technique is used to estimate an upper bound on excess lifetime cancer risk to exposed individuals, instead of populations. EPA's *Guidelines for Exposure Assessment* (EPA, 1992a) (not yet implemented) lists some of the questions that should be answered when considering individual versus population risk. These questions are stated by EPA as follows:

Individual Risk

- Are individuals at risk from exposure to the substances under study? Although for substances, such as carcinogens, that are assumed to have no threshold, only a zero dose would result in nonexcess risk for noncarcinogens, this

question can often be addressed. In the case of the use of hazard indices, where exposure or doses are compared to a reference dose or some other acceptable level, the risk descriptor would be a statement based on the ratio between the dose incurred and the reference dose.

- To what risk levels are the persons at the highest risk subjected? Who are these people, what are they doing, where do they live, etc., and what might be putting them at this higher risk?
- Can people with a high degree of susceptibility be identified?
- What is the average individual risk?

Population Risk

- How many cases of a particular health effect might be probabilistically estimated for a population of interest during a specified time period?
- For noncarcinogens, what portion of the population exceed the reference dose (RfD), the reference concentration (RfC), or other health concern level? For carcinogens, how many persons are above a certain risk level such as 10^{-6} or a series of risk levels such as 10^{-5}, 10^{-4}, etc.
- How do various subgroups fall within the distributions of exposure, dose, and risk?
- What is the risk for a particular population segment?
- Do any particular subgroups experience a high exposure, dose, or risk?

Description of Uncertainty

Analysis of the uncertainty associated with a health risk estimate involves each step of the risk-assessment process: it brings together the uncertainty in emissions and exposure estimates with that of the toxicity dose-response assessment. Table 5-1 lists the uncertainty issues to be addressed at each step of a health risk assessment. Uncertainty analysis can take place at the time of each of those analyses, but because it affects the eventual risk estimate, it is considered part of the final step of risk assessment—risk characterization.

Several recent documents illustrate EPA's current approach to the analysis of uncertainty associated with health risk assessment, including the Superfund document (EPA, 1989a), the background information document for NESHAPS for radionuclides (EPA, 1989b), the *Guidelines for Exposure Assessment* (EPA, 1992a), and the risk-characterization memorandum (Appendix B).

Superfund Risk-Assessment Guidance

The Superfund document provides guidance to EPA and other government employees and contractors who are risk assessors, risk-assessment reviewers, remedial project managers, or risk managers involved in Superfund-site cleanup.

TABLE 5-1 Uncertainty Issues To Be Addressed in Each Risk Assessment Step

A. *Hazard Identification:* What do we know about the capacity of an environmental agent for causing cancer (or other adverse effects) in laboratory animals and in humans?
   1. the nature, reliability, and consistency of the particular studies in humans and in laboratory animals;
   2. the available information on the mechanistic basis for activity; and
   3. experimental animal responses and their relevance to human outcomes.

B. *Dose-Response Assessment:* What do we know about the biological mechanisms and dose-response relationships underlying any effects observed in the laboratory or epidemiology studies providing data for the assessment?
   1. relationship between extrapolation models selected and available information on biological mechanisms;
   2. how appropriate data sets were selected from those that show the range of possible potencies both in laboratory animals and humans;
   3. basis for selecting interspecies dose scaling factors to account for scaling dose from experimental animals to humans; and,
   4. correspondence between the expected route(s) of exposure and the exposure route(s) utilized in the hazard studies, as well as the interrelationships of potential effects from different exposure routes.

C. *Exposure Assessment:* What do we know about the paths, patterns, and magnitudes of human exposure and number of persons likely to be exposed?
   1. The basis for the values and input parameters used in each exposure scenario. If based on data, information on the quality, purpose, and representatives of the database is needed. If based on assumptions, the source and general logic used to develop the assumption (e.g., monitoring, modeling, analogy, professional judgment) should be described.
   2. The major factor or factors (e.g., concentration, body uptake, duration/ frequency of exposure) thought to account for the greatest uncertainty in the exposure estimate, due either to sensitivity or lack of data.
   3. The link of the exposure information to the risk descriptors. These risk descriptors should include: (1) individual risk including the central tendency and high end portions of the risk distribution, (2) important subgroups of the population such as highly exposed or highly susceptible groups or individuals (if known), and (3) population risk. This issue includes the conservatism or non-conservatism of the scenarios, as indicated by the choice of descriptors. In addition, information that addresses the impact of possible low probability but possibly high consequence events should be addressed.
      For individual risk, information such as the people at highest risk, the risk levels these individuals are subject to, the activities putting them at higher risk, and the average risk for individuals in the population of interest should be addressed. For population risk, information as to the number of cases of a particular health effect that might be probabilistically estimated in this population for a specific time period, the portion of the population that are within a specified range of some benchmark level for non-carcinogens; and, for carcinogens, the number of persons above a certain risk level should be included. For subgroups, information as to how exposure and risk impact the various subgroups and the population risk of a particular subgroup should be provided.

D. *Risk Characterization:* What do other assessors, decision-makers, and the public need to know about the primary conclusions and assumptions, and about the balance between confidence and uncertainty in the assessment? What are the strengths and limitations of the assessment?

1. Numerical estimates should never be separated from the descriptive information that is integral to the risk assessment. For decisionmakers, a complete characterization (key descriptive elements along with numerical estimates) should be retained in all discussions and papers relating to an assessment used in decision-making. Differences in assumptions and uncertainties, coupled with non-scientific considerations called for in various environmental statutes, can clearly lead to different risk management decisions in cases with ostensibly identical quantitative risks; i.e., the "number" alone does not determine the decisions.
2. Consideration of alternative approaches involves examining selected plausible options for addressing a given uncertainty. The strengths and weaknesses of each alternative approach and as appropriate, estimates of central tendency and variability (e.g., mean, percentiles, range, variance). The description of the option chosen should include the rationale for the choice, the effect of option selected on the assessment, a comparison with other plausible options, and the potential impacts of new research.

SOURCE: Risk-characterization memorandum (Appendix B).

Section 8.4 of the document "discusses practical approaches to assessing uncertainty in Superfund site risk assessments and describes ways to present key information bearing on the level of confidence in quantitative risk estimates for a site." The document considers three categories of uncertainty associated with site risk assessments: selection of substances, toxicity values, and exposure assessments. Table 5-2 is EPA's uncertainty checklist for Superfund-site risk assessments. Risk assessors are to use the checklist to ensure that they describe adequately the uncertainty in a risk assessment. The document indicates that, although the uncertainty associated with each variable in a risk assessment would ideally be associated with the final risk estimate, a more practical approach is to describe qualitatively how the uncertainties might be magnified or the estimates of risk biased because of the risk models used. This document is being updated.

Uncertainty Analysis for Radionuclide Risk

EPA undertook a more comprehensive, integrated, quantitative approach to uncertainty characterization in the background document for its environmental impact statement on the National Emission Standards for Hazardous Air Pollutants (NESHAPS) for radionuclides (EPA, 1989b). This document includes an extensive presentation of estimates of fatal cancer risks associated with exposure to radionuclides. The estimates were "intended to be reasonable best estimates of risk; that is, to not significantly underestimate or overestimate risks and be of

TABLE 5-2 EPA Guidance for Uncertainty Analysis in Superfund Risk Assessments

LIST PHYSICAL SETTING DEFINITION UNCERTAINTIES

- For chemicals not included in the quantitative risk assessment, describe briefly:
  - — reason for exclusion (e.g., quality control), and
  - — possible consequences of exclusion on risk assessment (e.g., because of widespread contamination, underestimate of risk).
- For the *current land uses* describe:
  - — sources and quality of information, and
  - — qualitative confidence level.
- For the *future land uses* describe:
  - — sources and quality of information, and
  - — information related to the likelihood of occurrence.
- For *each exposure pathway*, describe why pathway was selected or not selected for evaluation.

  For *each combination of pathways*, describe any qualifications regarding the selection of exposure pathways considered to contribute to exposure of the same individual or group of individuals over the same period of time.

CHARACTERIZE MODEL UNCERTAINTIES

- List/summarize the key model assumptions.
- Indicate the potential impact of each on risk:
  - — direction (i.e., may over- or underestimate risk); and
  - — magnitude (e.g., order of magnitude).

CHARACTERIZE TOXICITY ASSESSMENT UNCERTAINTIES

For each substance carried through the quantitative risk assessment, list uncertainties related to:

- qualitative hazard findings (i.e., potential for human toxicity);
- derivation of toxicity values, e.g.,
  - — human or animal data,
  - — duration of study (e.g., chronic study used to set subchronic RfD), and
  - — any special considerations;
- the potential for synergistic or antagonistic interactions with other substances affecting the same individuals; and
- calculation of lifetime cancer risks on the basis of less-than-lifetime exposures.

For each substance not included in the quantitative risk assessment because of inadequate toxicity information, list:

- possible health effects; and
- possible consequences of exclusion on final risk estimates.

RISK CHARACTERIZATION

- confidence that the key site-related contaminants were identified and discussion of contaminant concentrations relative to background concentration ranges;

- a description of the various types of cancer and other health risks present at the site (e.g., liver toxicity, neurotoxicity), distinguishing between known effects in humans and those that are predicted to occur based on animal experiments;
- level of confidence in the quantitative toxicity information used to estimate risks and presentation of qualitative information on the toxicity of substances not included in the quantitative assessment;
- level of confidence in the exposure estimates for key exposure pathways and related exposure parameter assumptions;
- the magnitude of the cancer risks and noncancer hazard indices relative to the Superfund site remediation goals in the NCP (e.g., the cancer risk range of 10^{-4} to 10^{-7} and noncancer hazard index of 1.0);
- the major factors driving the site risks (e.g., substances, pathways, and pathway combinations);
- the major factors reducing the certainty in the results and the significance of these uncertainties (e.g., adding risks over several substances and pathways);
- exposed population characteristics; and
- comparison with site-specific health studies, when available.

SOURCE: Adapted from EPA, 1989a.

sufficient accuracy to support decisionmaking" (EPA, 1989b). One chapter of the document, however, provides a detailed analysis of uncertainties in the calculated risks that was undertaken by EPA's Office of Radiation Programs for four selected exposure sites, such as a uranium-mill tailings pile in Washington and an elemental-phosphorus plant in Idaho. The stated reason for the uncertainty analysis was that "quantitative uncertainty analysis can provide results that indicate the likelihood of realizing different risk levels across the range of uncertainty. This type of information is very useful for incorporating acceptable and reasonable confidence levels into decisions" (EPA, 1989b).

The EPA uncertainty analysis for radionuclide risks focused on "parameter uncertainty," because it was felt that other sources of uncertainty involving alternative or additional exposure pathways and risk-model structures were "not readily amenable to explicit analysis" (EPA, 1989b). Parameter uncertainties were first modeled as particular probability distributions for each parameter involved in four key components of the radionuclide risk assessments: source terms, atmospheric-dispersion factors, environmental-transport and radionuclide-uptake factors, and risk-conversion (that is, radionuclide-potency) factors. All the distributions pertaining to exposure-related factors were intended to model uncertainty in factor values characteristic of a maximally exposed person. All the distributions pertaining to uptake-related factors were intended to model uncertainty in factor values characteristic of an average individual, except in a set of separate corresponding analyses in which census-based interindividual variability

in home-residence time was incorporated into the analysis, where it was computationally treated as an uncertain parameter.

Monte Carlo methods were used to propagate uncertainty within contamination-uptake-risk models for calculating radionuclide-specific, increased lifetime risks of fatal cancer to an otherwise typical person who is maximally exposed over a lifetime (70 years) or over some shorter period sampled randomly from the distribution used to characterize home-residence time. The resulting characterization obtained for uncertainty in estimated total increased fatal-cancer risk associated with potential maximal exposure to all radionuclides for an exposure scenario involving a uranium-mill tailings pile is shown in Figure 5-1. The horizontal axis in that figure represents increased risk multiplied by 3.5×10^{-6}, which is the geometric mean of the distribution (shown as the solid curve) of risk to an individual maximally exposed for 70 years. (Normalization to the geometric mean value was done simply because all the risk distributions obtained were very close to lognormal.)

The vertical axis in Figure 5-1 represents cumulative probability expressed as a percentage, that is, the probability that the true (but certain) risk is less than or equal to a given, corresponding particular risk value shown on the horizontal axis. The solid horizontal line in the figure corresponds to cumulative probability equal to 50%. The dashed curve in the figure represents estimated risk accounting for less-than-lifetime home residence. In commenting on the substantial difference between the solid and dashed curves for the four types of exposure scenarios considered in this uncertainty analysis, EPA concluded that "it is clear … that many moves are to nearby locations," that "we do not believe that including a factor for exposure duration improves the assessment of maximum individual risk," and that "improper application of such a factor can easily lead to erroneous conclusions regarding uncertainties in the risk assessment" (EPA, 1989b).

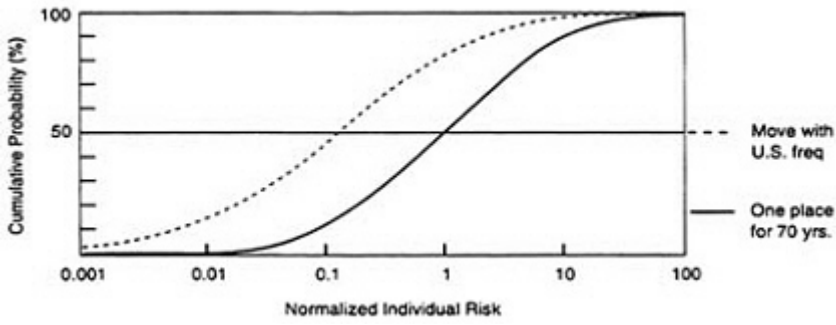


FIGURE 5-1 Uncertainty in estimated total increased fatal-cancer risk associated with potential maximal exposure to all radionuclides for an exposure scenario involving a uranium-mill tailings pile.
SOURCE: Adapted from EPA, 1989b.

Presentation of Risk Estimates

Several methods can be used to display health risk estimates. Some of the terms used most often are listed in Table 5-2. The definitions are from the new 1992 exposure guidelines (EPA, 1992a). Any combination of them can be used to display the risk estimate to either the risk manager or the public. The choice of descriptors is often based on legal mandates. In general, the display includes a table indicating the risk estimated for the exposed population by route of exposure.

1992 Exposure-Assessment Guidelines

EPA's 1992 *Guidelines for Exposure Assessment* shows a clear presentation of hazard-identification, dose-response, and exposure-assessment information that might be useful in future risk assessments. Risk assessors are to examine the judgments made during the process, the constraints of available data, and the state of knowledge. According to EPA, the risk characterization should include (EPA, 1992a)

- the qualitative, weight-of-evidence conclusions about the likelihood that the chemical may pose a specific hazard (or hazards) to human health, the nature and severity of the observed effects, and by what route(s) these effects are seen to occur. These judgments affect both the dose-response and exposure assessments.
- for noncancer effects, a discussion of the dose-response behavior of the critical effect(s), data such as the shapes and slopes of the dose-response curves for the various other toxic end points, and how this information was used to determine the appropriate dose-response assessment techniques; and
- the estimates of the magnitude of the exposure, the route, duration and pattern of the exposure, relevant pharmacokinetics, and the number and characteristics of the population exposed. This information must be compatible with both the hazard identification and dose-response assessments.

The risk-characterization summary should highlight the key points of each step of the risk-assessment process.

Risk-Characterization Memorandum

EPA is in transition on risk characterization. Besides the exposure guidelines described above, the risk-characterization memorandum (Appendix B) provides guidance on risk characterization and uncertainty analysis for EPA risk managers and risk assessors. The memorandum

> addresses a problem that affects public perception regarding the reliability of EPA's scientific assessments and related regulatory decisions… Significant information is often omitted as the results of the assessment are passed along in the decision-making process. … Often, when risk information is presented to

the ultimate decision-maker and to the public, the results have been boiled down to a point estimate of risk. Such "short hand" approaches to risk assessment do not fully convey the range of information considered and used in developing the assessment. In short, informative risk characterizations clarified the scientific basis for EPA decisions, while numbers alone do not give a true picture of the assessment.

A statement attached to the memorandum from the Risk Assessment Council, made up of EPA senior managers, emphasized the following principles:

- *Full Characterization of Risk:* A full and open discussion of uncertainties in the body of each EPA risk assessment, including prominent display of critical uncertainties in the risk characterization. Numerical risk estimates should always be accompanied by descriptive information carefully selected to ensure an objective and balanced characterization of risk in risk assessment reports and regulatory documents.
- *Comparability and Consistency:* confusion as to the comparability of similar looking (but quite different) risks, for example, the risk estimate for an average individual risk relative to the risk estimate for the most exposed individual, have led to misunderstandings about the relative significance of risks and the protectiveness of risk, reduction action. Therefore, several different descriptors of risk as outlined in the newly revised *Exposure Assessment Guidelines,* should be presented to provide a more complete picture of the risk than available from a single descriptor of risk.
- *Professional Judgment:* There are limits to the degree to which a full characterization of risk may be provided. The degree to which confidence and uncertainty are addressed depends largely on the scope of the assessment and available sources. So decision-makers and the public are not overwhelmed, only the most significant data and uncertainties need be presented. Further, when special circumstances (e. g., lack of data, extremely complex situations, resource limitations, statutory deadlines) preclude an assessment, such circumstances should be explained.

In implementing that guidance, EPA staff should:

1. Clearly present risk assessment information separate from any non-scientific risk management considerations.
2. Key scientific information on data and methods (e.g., use of animal or human data for extrapolating from high to low doses, use of pharmacokinetics data) must be highlighted, and a statement of confidence in the assessments that identifies all major uncertainties along with comment on their influence on the assessment must be provided.
3. The range of exposures derived from exposure scenarios and on the use of multiple risk descriptors (i.e., central tendency, high end of individual risk, population risk, important subgroups (if known) should be presented.

The risk-characterization memorandum goes through each step of risk assessment and outlines the questions to be answered. These are shown in Table 5-1, which suggests several issues that should be addressed to describe the information in each step fully.

Communication of Risk

Risk communication consists of two parts: communication between the risk assessor and the risk manager and communication between the risk-assessment management team and the public. The risk manager often receives the individual and population risk estimates (generally point estimates but occasionally ranges of these estimates) with only a qualitative description of the uncertainties in each. The general public often receives much less information—only the point estimate or range (without a description of the uncertainty) and the risk manager's decision—although far more is available from published sources or on request. In most regulatory situations, the manager's decision and supporting information are published in the *Federal Register*. In addition, extensive background documents that discuss the risk analysis in much more depth are often available to the public. The public is generally given an opportunity to comment within 30-60 days on the analysis and resulting decision. EPA may adjust a risk assessment on the basis of public comments.

Part II

Strategies for Improving Risk Assessment

Previous chapters have examined the various steps of the health risk-assessment process in the sequence developed by the 1983 Red Book committee. In considering the various steps to risk assessment, the committee observed that several common themes cut across the various stages of risk assessment and arise in criticisms of each individual step. These themes are as follows:

- *Default options*. Is there a set of clear and consistent principles for choosing and departing from default options?
- *Validation*. Has the Environmental Protection Agency (EPA) made a sufficient case that its methods and models for carrying out risk assessments are consistent with current scientific information available?
- *Data needs*. Is enough information available to EPA to generate risk assessments that are protective of public health and are scientifically plausible? What types of information should EPA obtain and how should the information best be used?
- *Uncertainty*. Has EPA taken sufficient account of the need to consider, describe, and make decisions in light of the inevitable uncertainty in risk assessment?
- *Variability*. Has EPA sufficiently considered the extensive variation among individuals in their exposures to toxic substances and in their susceptibilities to cancer and other health effects?
- *Aggregation*. Is EPA appropriately addressing the possibility of interactions among pollutants in their effects on human health, and addressing the consideration of multiple exposure pathways and multiple adverse health effects?

The "Red Book" paradigm should be supplemented by applying a cross-cutting approach that uses those themes. Such an approach could ameliorate the following problems in risk assessment as it is currently practiced within the agency:

- The differing opinions in the scientific community on the merits of particular scientific evidence and the resulting lack of credibility caused by periodic revisions of particular "risk numbers" (e.g., those for dioxin).
- The reluctance to incorporate new scientific information into risk assessments when it might (erroneously) appear to increase uncertainty.
- The incompatibility of various inputs to risk characterization, e.g., dose estimates in units that cannot be combined with more sophisticated dose-response evaluations, or hazard-identification evidence that cannot readily be integrated into potency assessment.
- The emphasis on theoretical modeling over measurement.
- The production of risk assessments that are either insufficiently informative or too detailed for the needs of risk managers, and the related problem of lack of clear signals to guide risk-assessment research.

Considering the six cross-cutting themes in the planning and analysis of risk assessment will not solve the problems of risk assessment by itself. Indeed, too much emphasis on a cross-cutting vision of risk assessment might create unanticipated problems. On balance, however, the view of risk assessment proposed in Chapters 6-11 will serve two important purposes: it will give the individual cross-cutting themes a more prominent place in the risk-assessment process, and it will encourage the gradual evolution of attempts to improve risk assessment from its current, somewhat piecemeal orientation to a more holistic one, with the goal of improving the precision, comprehensibility, and usefulness for regulatory decision-making of the *entire* risk-assessment process. Whatever conceptual framework is used, the committee believes that EPA must develop principles for choosing default options and for judging when and how to depart from them. This controversial issue is described in the next section.

The Need For Risk-Assessment Principles

Our scientific knowledge of hazardous air pollutants has numerous gaps. Hence, there are many uncertainties in the health risk assessments of those pollutants. Some of these can be referred to as model uncertainties—for example, uncertainties regarding dose-response model choices due to a lack of knowledge about the mechanisms by which hazardous air pollutants elicit toxicity. As discussed more fully in Chapter 6, EPA has developed "default options" to use when such uncertainties arise. These options are used in the absence of convincing scientific information on which of several competing models and theories is correct. The options are not rules that bind the agency; rather, they constitute

guidelines from which the agency may depart when evaluating the risks posed by a specific substance. The agency may also change the guidelines as scientific knowledge accumulates.

The committee, as discussed in Chapter 6, believes that EPA has acted reasonably in electing to issue default options. Without uniform guidelines, there is a danger that the models used in risk assessment will be selected on an ad hoc basis, according to whether regulating a substance is though to be politically feasible or according to other parochial concerns. In addition, guidelines can provide a predictable and consistent structure for risk assessment.

The committee believes that only the description of default options in a risk assessment is not adequate. We believe that EPA should have principles for choosing default options and for judging when and how to depart from them. Without such principles, departures from defaults could be ad hoc, thereby undercutting the purpose of the default options. Neither the agency nor interested parties would have any guidance about the quality or quantity of evidence necessary to persuade the agency to depart from the default options or the point (s) in the process at which to present that evidence.

Moreover, without an underlying set of principles, EPA and the public will have no way to judge the wisdom of the default options themselves. The individual default options inevitably vary in their scientific basis, foundation in empirical data, degree of conservatism, plausibility, simplicity, transparency, and other attributes. If defaults were chosen without conscious reference to these or other attributes, EPA would be unable to judge the extent to which they fulfill the desired attributes. Nor could the agency make intelligent and consistent judgment about when and how to add new default options when "missing defaults" are identified. In addition, the policies that underlie EPA's choice of risk-assessment methods would not be clear to the public and Congress—for example, it would be unclear whether EPA places the highest value on protecting public health, on generating scientifically accurate estimates, or on other concerns.

The committee has identified a number of objectives that should be taken into account when considering principles for choosing and departing from default options: protecting the public health, ensuring scientific validity, minimizing serious errors in estimating risks, maximizing incentives for research, creating an orderly and predictable process, and fostering openness and trustworthiness. There might be additional relevant criteria as well.

The choice of principles inevitably involves choosing how to balance such objectives. For instance, the most open process might not be the one that yields the result most likely to be scientifically valid. Similarly, the goal of minimizing errors in estimation might conflict with that of protecting the public health, inasmuch as (given the pervasiveness of uncertainty) achievement of the latter objective might involve accepting the possibility that a given risk assessment will overestimate the risk.

The committee therefore found it difficult to agree on what principles EPA should adopt. For example, the committee debated whether EPA should base its practices on "plausible conservatism"—that is, on attempting to use models that have support in the scientific community and that tend to minimize the possibility that risk estimates generated by these models will significantly underestimate true risks. The committee also discussed whether EPA instead should attempt as much as possible to base its practices on calculating the risk estimate most likely to be true in the light of current scientific knowledge. After extensive discussion, no consensus was reached on this issue.

The committee also concluded that the choice of principles to guide risk assessment, although it requires a knowledge of science and scientific judgment, ultimately depends on policy judgments, and thus is not an issue for specific consideration by the committee, even if it could agree on the substance of specific recommendations. The choice reflects decisions about how scientific data and inferences should be used in the risk-assessment process, not about which data are correct or about what inferences should be drawn from those data. Thus, the selection of principles inevitably involves choices among competing values and among competing judgments about how best to respond to uncertainty.

Many members contended that the committee ought not attempt to recommend principles, but should leave their formulation to the policy process. They concluded that weighing societal values is properly left to those who have been chosen, directly or indirectly, to represent the public. Indeed, in the view of these members, any recommendation by the committee would give the false impression that the choice of principles is ultimately an issue of science; noting the sharp differentiation that Congress made between the tasks of this committee and those of the Risk Assessment and Management Commission established by Section 303 of the Clean Air Act Amendments of 1990. That commission, rather than this committee, appears to have been intended to address issues of policy.

Other members contended that the committee should attempt to recommend principles. They urged that the choice of risk-assessment principles is one of the most important decisions to be made in risk assessment and one on which risk assessment experts, because of their expertise on the scientific issues related to the choice, ought to make themselves heard. They believe that the choice of principles is no more policy-laden than many other issues addressed by the committee, and that the decision not to recommend principles is itself a policy choice. They also note that the scientific elements involved in making the choice distinguish the selection of principles from other pure "policy" issues that the committee agreed not to address such as the use of cost-benefit methods or the implications of the psychosocial dimensions of risk perception.

The committee has decided not to recommend principles in its report. Instead, it has included in Appendix N papers by three of its members that offer various perspectives on the issue. One paper, by Adam Finkel, urges that EPA

should strive to advance scientific consensus while minimizing serious errors of risk underestimation, by adopting an approach of "plausible conservatism." The other, by Roger McClellan and Warner North, argues that EPA should promote risk assessments that reflect current scientific understanding. Those perspectives are not intended to reflect the total range of opinion among committee members on the subject, but are presented to illustrate the issues involved.

Reporting Risk Assessments

As already mentioned, uncertainties are pervasive in risk assessment. When uncertainty concerns the magnitude of a physical quantity that can be measured or inferred from assumptions (e.g., ambient concentration), it can often be quantified, as Chapter 9 suggests.

Model uncertainties result from an inability to determine which scientific theory is correct or what assumptions should be used to derive risk estimates. Such uncertainties cannot be quantified on the basis of data. Any expression of probability, whether qualitative (e.g., a scientist's statement that a threshold is likely) or quantitative (e.g., a scientist's statement that there is a 90% probability of a threshold), is likely to be subjective. Subjective quantitative probabilities could be useful in conveying the judgments of individual scientists to risk managers and to the public, but the process of assessing subjective probabilities is difficult and essentially untried in a regulatory context. Substantial disagreement and misunderstanding about the reliability of quantitative probabilities could occur, especially if their basis is not set forth clearly and in detail.

In the face of important model uncertainties, it may still be undesirable to reduce a risk characterization to a single number, or even to a range of numbers intended to portray uncertainty. Instead, EPA should consider giving risk managers risk characterizations that are both qualitative and quantitative and both verbal and mathematical.

If EPA takes this route, quantitative assessments provided to risk managers should be based on the principles selected by EPA. EPA might choose to require that a risk assessment be accompanied by a statement describing alternative assumptions presented to the agency that, although they do not meet the principles selected by EPA for use in the risk characterization, satisfy some lesser test (e.g., plausibility). For example, EPA generally assumes that no threshold exists for carcinogenicity and calculates cancer potency using the linearized multistage model as the default. Commenters to the agency on a specific substance might attempt to show that there is a threshold for that substance on the basis of what is known about its mechanism of action. If the threshold can be demonstrated in a manner that is satisfactory under the agency's risk-assessment principles, the risk characterization would be based on the threshold assumption. If such a demonstration cannot be made, then the risk characterization would be based on the no-threshold assumption; but if the threshold assumption were found to be

plausible, the risk manager might be informed of its existence as a plausible assumption, its rationale, and its effect on the risk estimate. In this way, risk assessors would receive both qualitative and quantitative information relevant to characterizing the uncertainty associated with the risk estimate.

The Iterative Approach

One strategy component that deserves emphasis is the need for iteration. Neither the resources nor the necessary scientific data exist to perform a full-scale risk assessment on each of the 189 chemicals listed as hazardous air pollutants by Section 112 of the Clean Air Act. Nor, in many cases, is such an assessment needed. Some of the chemicals are unlikely to pose more than a de minimis (trivial) risk once the maximum available control technology is applied to their sources as required by Section 112. Moreover, most sources of Section 112 pollutants emit more than one such pollutant, and control technology for Section 112 pollutants is rarely pollutant-specific. Therefore, there might not be much incentive for industry to petition EPA to remove substances from Section 112's list (or much need for EPA to devote its resources to carrying out risk assessments in response to such petitions).

An iterative approach to risk assessment would start with relatively inexpensive screening techniques and move to more resource-intensive levels of datagathering, model construction, and model application as the particular situation warranted. To guard against the possibility of underestimating risk, screening techniques must be constructed that err on the side of caution when there is uncertainty. (As discussed in Chapter 12, the committee has some doubts about whether EPA's current screening techniques are so constructed.) The results of such screening should be used to set priorities for gathering further data and applying successively more complex techniques. These techniques should then be used to the extent necessary to make a judgment. In Chapter 7, the kinds of data that should be obtained at each stage of such an iterative process are described. The result would be a process that yields the risk-management decisions required by the Clean Air Act and that provides incentives for further research without the need for costly case-by-case evaluations of individual chemicals. Use of an iterative approach can improve the scientific basis of risk-assessment decisions and account for risk-management concerns, such as the level of protection and resource constraints.

6

Default Options

EPA's risk-assessment practices rest heavily on "inference guidelines" or, as they are often called, "default options." These options are generic approaches, based on general scientific knowledge and policy judgment, that are applied to various elements of the risk-assessment process when the correct scientific model is unknown or uncertain. The 1983 NRC report *Risk Assessment in the Federal Government: Managing the Process* defined *default Option* as "the option chosen on the basis of risk assessment policy that appears to be the best choice in the absence of data to the contrary" (NRC, 1983a, p. 63). Default options are not rules that bind the agency; rather, as the alternative term *inference guidelines* implies, the agency may depart from them in evaluating the risks posed by a specific substance when it believes this to be appropriate. In this chapter, we discuss EPA's practice of adopting guidelines containing default options and departing from them in specific cases.

Adoption Of Guidelines

As our discussion of risk assessment has made clear, current knowledge of carcinogenesis, although rapidly advancing, still contains many important gaps. For instance, for most carcinogens, we do not know the complete relationship between the dose of a carcinogen and the risk it poses. Thus, when there is evidence of a carcinogenic effect at a high concentration (for instance, in the workplace or in animal testing), we do not know for certain how strong the effect (if any) would be at the lower concentrations typically found in the environment. Similarly, we do not know how much importance to attach to experiments that

show that exposure to a substance causes only benign tumors in animals or how to adjust for metabolic differences between animals and humans in calculating the carcinogenic potency of a chemical.

Other uncertainties are not peculiar to carcinogenesis, but are characteristic of many aspects of risk assessment. For example, calculating the doses received by individuals might require knowledge of the relationship between emission of a substance by a source and the ambient concentration of that substance at a particular place and time. It is impossible to install a monitor at every place where people might be exposed; moreover, monitoring results are subject to error. Thus, regulators attempt to use air-quality models to predict ambient concentrations. But because our knowledge of atmospheric processes is imperfect and the data needed to use the models cannot always be obtained, the predictions from atmospheric-transport models can differ substantially from measured ambient concentrations (NRC, 1991a).

In time, we hope, our knowledge and data will improve. Indeed, we believe that EPA and other government agencies must engage in scientific research and be receptive to the results of sound scientific research conducted by others. In the meantime, decisions about regulating hazardous air pollutants must be made under conditions of uncertainty. It is vital that the risk-assessment process handle uncertainties in a predictable way that is scientifically defensible, consistent with the agency's statutory mission, and responsive to the needs of decisionmakers.

These uncertainties, as we explain further in Chapter 9, are of two major types. One type, which we call *parameter uncertainty*, is caused by our inability to determine accurately the values of key inputs to scientific models, such as emissions, ambient concentrations, and rates of metabolic action. The second type, *model uncertainty*, is caused by gaps in our knowledge of mechanisms of exposure and toxicity—gaps that make it impossible to know for certain which of several competing models is correct. For instance, as mentioned above, we often do not know whether a threshold may exist below which a dose of a carcinogen will not result in an adverse effect. As we discuss in Chapter 9, model uncertainties, unlike parameter uncertainties, are often difficult to quantify.

The Red Book recommended that model uncertainties be handled through the development of uniform inference guidelines for the use of federal regulatory agencies in the risk-assessment process. Such guidelines would structure the interpretation of scientific and technical information relevant to the assessment of health risks. The guidelines, the report urged, should not be rigid, but instead should allow flexibility to consider unique scientific evidence in particular instances.

The Red Book described the advantages of such guidelines as follows (pp. 7-8):

> The use of uniform guidelines would promote clarity, completeness, and consistency in risk assessment; would clarify the relative roles of scientific and other factors in risk assessment policy; would help to ensure that assessments reflect the latest scientific understanding; and would enable regulated parties to anticipate government decisions. In addition, adherence to inference guidelines will aid in maintaining the distinction between risk assessment and risk management.

This committee believes that those considerations continue to be valid. In particular, we stress the importance of inference guidelines as a way of keeping risk assessment and risk management from unduly influencing each other. Without uniform guidelines, risk assessments might be manipulated on an ad hoc basis according to whether regulating a substance is thought to be politically feasible. In addition, we believe that inference guidelines can provide a predictable and consistent structure for risk assessment and that a statement of guidelines forces an agency to articulate publicly its approach to model uncertainty.

Like the committee that produced the 1983 NRC report, we recognize that there is an inevitable interplay between risk assessment and risk management. As the 1983 report states (pp. 76, 81), "risk assessment must always include policy, as well as science," and "guidelines must include both scientific knowledge and policy judgments." Any choice of defaults, or the decision not to have defaults at all, therefore amounts to a policy decision. Indeed, without a policy decision, the report stated, risk-assessment guidelines could do no more than "state the scientifically plausible inference options for each risk assessment component without attempting to select or even suggest a preferred inference option" (NRC, 1983a, p. 77). Such guidelines would be virtually useless. The report urged that risk-assessment guidelines include risk-assessment policy and explicitly distinguish between scientific knowledge and risk-assessment policy to keep policy decisions from being disguised as scientific conclusions (NRC, 1983a, p. 7). That report urged that for consistency, policy judgments related to risk assessment ought to be based on a common principle or principles.

We believe that EPA acted reasonably in electing to issue *Guidelines for Carcinogen Risk Assessment* (EPA, 1986a). Those guidelines set out policy judgments about the accommodation of model uncertainties that are used to assess risk in the absence of a clear demonstration that a particular theory or model should be used.

For instance, the default options indicate that, in assessing the magnitude of risk to humans associated with low doses of a substance, "in the absence of adequate information to the contrary, the linearized multistage procedure will be employed" (EPA, 1986a, p. 33997). The linearized multistage procedure implies low-dose linearity. At low doses, if the dose is reduced by, say, a factor of 1,000, the risk is also reduced by a factor of 1,000; dose is linearly related to risk. Departure from this default option is allowed, under EPA's current guidelines,

if there is "adequate evidence" that the mechanism through which the substance is carcinogenic is more consistent with a different model—for instance, that there is a threshold below which exposure is not associated with a risk. Thus, the default option in guiding a decision-maker, in the absence of evidence to the contrary, assigns the burden of persuasion to those who wish to show that the linearized multistage procedure should not be used. Similar default options cover such important issues as the calculation of effective dose, the treatment of benign tumors, and the procedure for scaling animal-test results to estimates of potency in humans.

Some default options are concerned with issues of extrapolation—from laboratory animals to humans, from large to small exposures (or doses), from intermittent to chronic lifetime exposures, and from route to route (as from ingestion to inhalation). That is because few chemicals have been shown in epidemiologic studies to cause measurable numbers of human cancers directly, and epidemiologic data on only a few of these are sufficient to support quantitative estimates of human epidemiologic cancer risk. In the absence of adequate human data, it is necessary to use laboratory animals as surrogates for humans.

One advantage of guidelines, as already noted, is that they can articulate both the agency's choice of individual default options and its rationale for choosing all of the options. EPA's guidelines set out individual options but do not do so with ideal clarity. Nor has the agency explicitly articulated the scientific and policy bases for its options. Hence, there might be disagreement about precisely what the agency's default options are and the rationales for these options. We attempt here to identify the most important of the options (numbered points in the 1986 guidelines are cited):

- Laboratory animals are a surrogate for humans in assessing cancer risks; positive cancer-bioassay results in laboratory animals are taken as evidence of a chemical's cancer-causing potential in humans (IV).
- Humans are as sensitive as the most sensitive animal species, strain, or sex evaluated in a bioassay with appropriate study-design characteristics (III.A.1).
- Agents that are positive in long-term animal experiments and also show evidence of promoting or cocarcinogenic activity should be considered as complete carcinogens (II.B.6).
- Benign tumors are surrogates for malignant tumors, so benign and malignant tumors are added in evaluating whether a chemical is carcinogenic and in assessing its potency (III.A.1 and IV.B.1).
- Chemicals act like radiation at low exposures (doses) in inducing cancer; i.e., intake of even one molecule of a chemical has an associated probability for cancer induction that can be calculated, so the appropriate model for relating exposure-response relationships is the linearized multistage model (III.A.2).
- Important biological parameters, including the rate of metabolism of

chemicals, in humans and laboratory animals are related to body surface area. When extrapolating metabolic data from laboratory animals to humans, one may use the relationship of surface area in the test species to that in humans in modifying the laboratory animal data (III.A.3).

- A given unit of intake of a chemical has the same effect, regardless of the time of its intake; chemical intake is integrated over time, irrespective of intake rate and duration (III.B).
- Individual chemicals act independently of other chemicals in inducing cancer when multiple chemicals are taken into the body; when assessing the risks associated with exposures to mixtures of chemicals, one treats the risks additively (III.C.2).

EPA has never articulated the policy basis for those options. As we discuss in the previous introductory section (Part II), the agency should choose and explain the principles underlying its choices to avoid the dangers of ad hoc decision-making. The agency's choices are for the most part intended to be conservative—that is, they represent an implicit choice by the agency, in dealing with competing plausible assumptions, to use (as default options) the assumptions that lead to risk estimates that, although plausible, are believed to be more likely to overestimate than to underestimate the risk to human health and the environment. EPA's risk estimates thus are intended to reflect the upper region of the range of risks suggested by current scientific knowledge.

EPA appears to use conservative assumptions to implement Congress's authorization in several statutes, including the Clean Air Act, for the agency to undertake preventive action in the face of scientific uncertainty (see, e.g., *Ethyl v. EPA*, 541 F.2d 1 (D.C. Cir.) (en banc), *certiorari denied* 426 U.S. 941 (1976), ratified by Section 401 of the Clean Air Act Amendments of 1977) and to set standards that include a precautionary margin of safety against unknown effects and errors in calculating risks (see *Environmental Defense Fund v. EPA*, 598 F.2d 62, 70 (D.C. Cir. 1978) and *Natural Resources Defense Council v. EPA*, 824 F.2d 1146, 1165 (en banc) (D.C. Cir. 1987)).

EPA's choice of defaults has been controversial. We note, though, that some of the arguments about EPA's practices are directed less at conservatism than at the means of implementation that the agency has adopted. We believe that the iterative approach recommended in the previous chapter combined with quantitative uncertainty analysis will improve the agency's practices regardless of the degree of conservatism chosen by the agency. We also note that with an iterative approach, the agency must use relatively conservative models in performing screening estimates designed to indicate whether a pollutant is worthy of further analysis and comprehensive risk assessment. Such estimates are intended to obviate the detailed assessment of risks that can with a high degree of confidence be deemed acceptable or de minimis (trivial). By definition, therefore, screening analyses must be sufficiently conservative to make sure that a pollutant that could pose dangers to health or welfare will receive full scrutiny.

Over time, the choice of defaults should have decreasing impact on regulatory decision-making. As scientific knowledge increases, uncertainty diminishes. Better data and increased understanding of biological mechanisms should enable risk assessments that are less dependent on default assumptions and more accurate as predictions of human risk.

In evaluating EPA's risk-assessment methods, we are aware that the agency's guidelines, to use the terminology of the earlier NRC report, are in part statements of science policy, rather than purely statements of scientific fact. The guideline cited above dealing with extrapolation of high doses to low doses is illustrative. The guideline is not a claim that it is known that the relationship between dose and response is linear; that the true relationship between dose and response is uncertain and could be nonlinear is readily acknowledged. Rather, the guideline is based (1) on the scientific conclusion that the linear model has substantial support in current data and biologic theory and that no alternative model has sufficient support to warrant departure from the linear model for most chemicals identified as carcinogens; (2) on the further scientific conclusion that the linear model is more conservative than most alternative plausible models; and (3) on the policy judgment that a conservative model should be chosen when there is model uncertainty.

Departures From Default Options

Agency policies should encourage further scientific research. Risk assessors and managers must be receptive to new scientific information about the character and magnitude of the toxic effects of a chemical substance. Putting this receptivity into practice, though, has proved difficult. The 1983 NRC report criticized how agencies had implemented their guidelines. The report noted that "the application of inference options to specific risk assessments has been marked by a general lack of explicitness" and that that made it "difficult to know whether assessors adhere to guidelines" (NRC, 1983a, p. 79). The NRC report recognized the need to prevent ad hoc and undocumented departures from guidelines in specific risk assessments. But the NRC report made it clear that well-designed guidelines "should permit acceptance of new evidence that differs from what was previously perceived as the general case, when scientifically justifiable." NRC urged a recognition of the need for a tradeoff between flexibility on the one hand and predictability and consistency on the other (NRC, 1983a, p. 81).

The NRC advocated that agencies seek a middle path between inflexibility and ad hoc judgments, but steering this course is difficult. Consistency and predictability are served if an agency sets out criteria for departing from its guidelines. If such criteria are themselves too rigidly applied, the guidelines could ossify into inflexible rules; but without such criteria, the guidelines could be subverted at will with the potential for political manipulation of risk assessment.

NRC's approach requires that agencies regard their inference options not as binding rules, but rather as guidelines that are to be followed unless a sufficient showing is made. In the decade since the NRC report, EPA has never articulated clearly its criteria for a departure. We believe that a structured approach would give better guidance to the scientific community and to the public and would ensure both that the default options are set aside only when there is a valid scientific reason for doing so and that decisions to set aside defaults are scientifically credible and receive public acceptance.

EPA's practice appears to be to allow departure in a specific case when it ascertains that there is a consensus among knowledgeable scientists that the available scientific evidence justifies departure from the default option. The agency apparently considers both the quality of the data submitted and the robustness of the theory that is used to justify the departure.

EPA needs to be more precise in describing the kind and strength of evidence that it will require to depart from a default option. Because the decision as to the evidentiary burden to be required is ultimately one of policy, and because we could not reach agreement on proposed language to implement such a standard (see Appendixes N-1 and N-2), we do not urge any particular standard; moreover, we are conscious of the difficulties of capturing the nuances of judgment in any verbal formula that will not be open to misinterpretation.

We believe that the agency must continue to rely on its Science Advisory Board (SAB) and other expert bodies to determine when departing from a default option is warranted according to default options EPA will develop. EPA has increasingly used peer review and workshops as a way to ensure that it carefully considers the propriety of departing from a default. These and other devices should continue to ensure broad peer and scientific participation to guarantee, as much as possible, that the agency's risk-assessment decisions are made with access to the best science available.

We note that here, too, EPA has a difficult path to tread. EPA has been criticized for delay in deciding whether to depart from default options. Increased procedural formality raises the possibility of further delays, especially in a period of budgetary stringency such as EPA can expect to face for some time. It is likely that EPA will be cutting back on hiring personnel at the salary ranks necessary to attract scientists with the needed experience and training to judge whether departure from a default option is justifiable. Congress ought to be aware of the need for greater agency resources to carry out the mandates of the Clean Air Act and similar legislation.

Even if a default option is not set aside, we believe that decision-makers ought to be informed in a narrative way of any specific information suggesting that, in specific cases, alternatives to the default options might have equal or greater scientific support, and believe that the characterization of risk should include a discussion of the effect of the alternative options on risk estimates.

Current Epa Practice In Departing From Default options

As discussed above, EPA needs simultaneously to be receptive to evidence indicating the need to depart from a default option and to be careful that it departs from a default in a specific case only when a departure is justifiable. In addition, the agency needs to follow a process that allows peer participation and review.

We discuss below some of the cases in which EPA has addressed the issue of whether to depart from default options. In each of these cases, EPA decisions to depart from default options lessened its estimate of the risk; however, it is important to note that new scientific data could also increase the estimate of risk above that reached by using the default options.

Example 1: Use of Animal-Cancer Bioassay Data

The example that follows illustrates a departure from the two default options that: (1) positive animal-bioassay results for cancer induction are sufficient proof of cancer hazard in humans; and (2) humans are at least as sensitive as the most sensitive responding animal species. It involves induction of kidney cancer in male laboratory rats by a number of chemicals—most important, 1,4-dichlorobenzene, hexachloroethane, isophorone, tetrachloroethylene, dimethyl methyl phosphorate, d-limonene, pentachloroethane, and unleaded gasoline (EPA, 1991d). The first four have been classified as hazardous air pollutants by the Clean Air Act Amendments of 1990.

Male rats exposed to those chemicals develop dose-related kidney cancer; the highest incidence is usually 25% or less. The tumors do not occur in other organs or other species or in female rats. Because of the economic importance of several of the compounds and unleaded gasoline, extensive studies were conducted to understand the mechanisms involved in the development of the tumors. The studies suggested that a special mechanism was responsible for the tumors in male rats. When the chemicals in question are inhaled by male rats, the chemicals, or products of their metabolism, reach the bloodstream and form complexes with a specific protein, alpha-2μ-globulin, that is produced in the male rat liver and removed from the blood by the kidneys. As the complex is cleared from the blood by the kidneys, it accumulates there in the form of hyaline droplets, which lead to the development of kidney disease characterized by cell death, cast formation, mineralization, and hyperplasia. This accumulation, as well as statistically significant increases in tumors that result from exposure to the chemicals, occurs only in male rats.

In contrast, female rats, which do not have the same concentrations of alpha-2 μ-globulin protein, do not develop statistically significant increases tumors as a result of exposure. Similarly, the protein is not present in detectable quantities

in humans, so no risk of kidney-cancer development by this mechanism would be expected in humans exposed to the chemicals in question. It was therefore suggested that, inasmuch as a special mechanism not found in humans seemed to be responsible for the tumors, EPA ought to depart in this case from its default option that a substance that is carcinogenic in animals is also a human carcinogen. In response, EPA (1991d) evaluated the evidence of production of kidney tumors in male rats by chemicals inducing alpha-2μ-globulin accumulation (CIGAs), such as those in question. EPA's review suggested that kidney cancer in male rats from exposure to CIGAs is due only to the kidney disease that CIGAs cause through accumulation of alpha 2μ-globulin. For instance, EPA noted, the CIGAs are not known to react with DNA and are generally negative in short-term tests for genotoxicity. In contrast, classical kidney carcinogens (or their active metabolites) are usually electrophilic species that bind covalently to macromolecules and form DNA adducts. With the classical kidney carcinogens, which presumably are carcinogenic in both laboratory animals and humans, the kidney carcinogenesis is presumed to result from the interaction of the compounds or their metabolites with DNA. Classical kidney carcinogens, such as dimethylnitrosamine, induce renal tubule cancer in laboratory animals at a high incidence in both sexes after short periods of exposure, with a clear increase in kidney tumor incidence with increased dose. Thus, the classical kidney carcinogens and CIGAs appear to act via different mechanisms.

After reviewing the data, EPA (1991d) provided specific decision criteria for categorizing a chemical as a CIGA. A substance may be so classified only if it meets all the decision criteria, and classification of a chemical as a CIGA does not keep it from being considered as a carcinogen because of other modes of action. In that way, the agency precisely tailored its proposed departure from default options. EPA concluded that renal tubule tumors in male rats attributable solely to chemically induced alpha-2μ-globulin accumulation should not be used for human-cancer hazard identification or for dose-response extrapolations. Furthermore, EPA noted that even in the absence of renal tubule tumors in the male rat, if the lesions of alpha-2μ-globulin syndrome are present, the associated nephropathy in male rats should not contribute to determinations of noncarcinogenic hazard or risk.

EPA's documents reviewed and synthesized the available scientific information in a document that was then presented to peers in a public meeting, reviewed by the SAB's Environmental Health Committee and later endorsed by the SAB Executive Committee, and transmitted to the administrator (EPA, 1991d). Transmission to the administrator was accompanied by endorsement by the SAB that the document outlined a scientifically sound policy for departing from the default option for this specific class of compounds. This policy has been generally supported by the scientific community. However, it is noteworthy that some researchers (see, e.g., Melnick, 1992) believe that another mechanism to explain all of the observed data is equally or more plausible than the one

EPA endorsed. Alpha-2μ-globulin may be a carrier protein that transports certain chemicals to the kidney, where toxic metabolites can be released; this mechanism defines alpha-2μ-globulin accumulation as an *indicator* , rather than the *cause* of renal toxicity. If so, humans may have other carrier proteins that could transport toxins to the kidney and cause toxicity or carcinogenicity in the absence of protein droplet information, and the assumption that the rat studies are irrevelant to humans might therefore be erroneous.

Example 2: Linkages Between Exposure, Dose, and Response

In the previous example, a departure from default options occurred at the hazard-identification stage. As discussed in examples 2 and 3, such departures can also be used to refine the unit risk estimate of a carcinogen.

Calculating the unit risk through quantitative risk assessment requires an understanding of the relationship between exposure to a substance and response. One part of this relationship involves the link between exposure (that is, intake of a substance) and dose (that is, the amount of the substance, or harmful metabolites, that is taken up by bodily organs). However, that understanding is incomplete. EPA's default options assume that all species are equally sensitive to a given target-tissue dose of the toxicant or its metabolites. The surface-to-area ratios in the test species and humans are used as the key to relating the dose received by the test species to the dose that would cause similar effects in humans (see pp. 6-7, III.A.3). As the following examples show, however, evidence can sometimes support departing from this default option.

Methylene Chloride

Epidemiological studies on whether exposure to methylene chloride causes cancer in humans have produced equivocal results. Thus, assessment of methylene chloride's carcinogenic risk depends on use of laboratory animal data and especially on several long-term bioassays. Syrian hamsters did not show a tumor response at any site at exposures up to 3,500 ppm for 6 hr/day 5 days/week, but mice and rats exposed at up to 4,000 ppm for 6 hr/day 5 days/week had treatment-related tumorigenic effects. EPA, after evaluating the data, classified methylene chloride as a probable human carcinogen (B2).

In accord with the default options of EPA's guidelines, the carcinogenic potency of methylene chloride was estimated by scaling the laboratory animal data to humans with a body surface-area conversion factor. The resulting cancer risk estimate was 4.1×10^{-6} for exposure at 1 $\mu g/m^3$ (Table 6-1). After further consideration, EPA has decreased this estimate by an order of magnitude (EPA, 1991d). The reduction is based on research on the pathways through which methylene chloride is metabolized. As with some other carcinogens, the risk of cancer arises not from methylene chloride itself, but rather from its metabolites.

TABLE 6-1 Cancer Incidence in B6C3F1 Female Mice Exposed to Methylene Chloride and Human Cancer Risk Estimates Derived from Animal Data

Animal Data				
Concentration, Administered	Transformed Animal mg/kg, day	Human Equivalent mg/kg, day	Incidence of Liver Tumors	Incidence of Lung Tumors
4000	3162	712	40/46	41/46
2000	1582	356	16/46	16/46
0	0	0	3/45	3/45
Human Risk Estimates				
Extrapolation Model			Cancer Risk[b] for 1 μg/m^3	
LMS[a] , surface area			4.1×10^{-6}	
LMS, PB-PK[c]			3.7×10^{-8}	
Logit			2.1×10^{-13}	
Weibull			9.8×10^{-8}	
Probit			$<10^{-15}$	
LMS-PB-PK with scaling for sensitivity			4.7×10^{-7}	

[a] LMS = linearized multistage model.
[b] Upper 95% confidence limit.
[c] PB-PK = physiologically based pharmacokinetic.
SOURCE: Modified from Reitz et al., 1989.

A correct calculation of the risk posed by methylene chloride therefore rests on understanding the human body's processes for metabolizing this chemical.

Research with animal species used in the bioassays and human tissue has shed light on the metabolism of methylene chloride. Much of the research was conducted with the goal of providing input for physiologically based pharmacokinetic (PBPK) models (Andersen et al., 1987, 1991; Reitz et al., 1989). The data were modeled in various ways, including consideration of two metabolic pathways. One involves oxidation by mixed-function oxidase (MFO) enzymes, and the other involves a glutathione*S*-transferase (GST). Both pathways involve the formation of potentially reactive intermediates: formyl chloride in the MFO pathway and chloromethyl glutathione in the GST-mediated pathway. The MFO pathway was modeled as having saturable, or Michaelis-Menten, kinetics, and the GST pathway as a first-order reaction, i.e., proportional to concentration. The analyses suggested that a reactive metabolite formed in the GST pathway

was responsible for tumor formation. This pathway, according to the analyses, contributes importantly to the disposition of methylene chloride only at exposures that saturate the primary MFO pathway. The analyses further indicated that the GST pathway is less active in human tissues than in mice. This suggests that the default option of scaling for surface area yields a human risk estimate that is too high to be plausible. EPA incorporated the data on pharmacokinetics and metabolism into its most recent risk assessment for methylene chloride, although it retained a surface-area correction factor—now identifying it as a correction for interspecies differences in sensitivity. The new risk estimate is 4.7×10^{-7} for continuous exposure at 1 $\mu g/m^3$ (Table 6-1).

The process by which EPA arrived at the current risk estimate for methylene chloride with PBPK modeling involved use of peer-review groups and SAB review to achieve a scientifically acceptable consensus position on the validity of the alternative model. After EPA's re-evaluation, however, articles in the peer-reviewed literature began to focus attention on parameter uncertainties in PBPK modeling, which neither EPA nor the original researchers in the methylene chloride case had considered. In the specific case of methylene chloride, at least one of the analyses (Portier and Kaplan, 1989) suggested that according to the new PBPK information EPA should have raised, rather than lowered, its original unit risk estimate if it wanted to continue to take a conservative stance. The more general point, which we discuss in Chapter 9, is that EPA must simultaneously consider both the evidence for departing from default models and the need to generate or modify the parameters that drive both the alternative and default models.

Formaldehyde

The toxicity and carcinogenicity of formaldehyde, a widely used commodity chemical, have been intensely studied and recently reviewed (Heck et al., 1990; EPA, 1991e). Concern for the potential human carcinogenicity of formaldehyde was heightened by the observation that exposure of rats at high concentrations (14.3 ppm) resulted in a very large increase in the incidence of nasal cancer. That observation gave impetus to the conduct and interpretation of epidemiologic studies of formaldehyde-exposed human populations. In the aggregate, the 28 studies that have been reported provide limited evidence of human carcinogenicity (EPA, 1991e). The "limited" classification is used primarily because the incidence of cancers of the upper respiratory tract has been confounded by exposure to other agents known to increase the rate of cancer, such as cigarette smoke and wood dusts.

The effects of chronic inhalation of formaldehyde have been investigated in rats, mice, hamsters, and monkeys. The principal evidence of carcinogenicity comes from studies in both sexes and two strains of rats and the males of one strain of mice, all showing squamous cell carcinomas of the nasal cavity.

The results of the rat bioassay have been used to derive quantitative risk estimates for cancer induction in humans (Kerns et al., 1983). Table 6-2 shows these animal data and the estimates of human cancer risk based on different exposure-dose models. (The table uses the inhalation cancer unit risk—the lifetime risk of developing cancer from continuous exposure at 1 ppm.) The 1987 EPA risk estimate (EPA, 1987c) measured exposure as the airborne concentration of formaldehyde. The rat bioassay shows a steep nonlinear exposure-response relationship for nasal-tumor induction. For example, two tumors were observed at 5.6 ppm, whereas 37 would have been expected from linear extrapolation from 14.3 ppm. Similarly, no tumors were observed at 2 ppm, whereas linear extrapolation from 14.3 ppm would have predicted 15.

The key issue became whether the same exposure-response relationship exists in people as in rats. To determine the answer, researchers directed substantial effort toward investigating the mechanisms by which formaldehyde exerted a carcinogenic effect. One avenue of investigation was directed toward characterizing

TABLE 6-2 Incidence of Nasal Tumors in F344 Rats Exposed to Formaldehyde and Comparison of EPA Estimates of Human Cancer Risk Associated with Continuous Exposure to Formaldehyde

	Exposure rate, ppm[a]	Incidence of Rat Nasal Tumors	
	14.3	94/140	
	5.6	2/153	
	2.0	0/159	
	0	0/156	
	Upper 95% Confidence Limit Estimates		
Exposure Concentration, ppm	1987 Risk Estimates[b]	1991 Risk Estimates[c]	
		Monkey-Based	Rat-Based
1.0	2×10^{-2}	7×10^{-4}	1×10^{-2}
0.5	8×10^{-3}	2×10^{-4}	3×10^{-3}
0.1	2×10^{-3}	3×10^{-5}	3×10^{-4}
	Maximum Likelihood Estimates		
1.0	1×10^{-2}	1×10^{-4}	1×10^{-2}
0.5	5×10^{-4}	1×10^{-5}	1×10^{-3}
0.1	5×10^{-7}	4×10^{-7}	3×10^{-5}

[a] Exposed 6 hr/day, 5 days/week for 2 years.

[b] Estimated with 1987 inhalation cancer unit risk of 1.6×10^{-2} per ppm, which used airborne concentration as measure of exposure.

[c] Estimated with 1991 inhalation cancer unit risks of 2.8×10^{-3} per ppm (rat) and 3.3×10^{-4} per ppm (monkey), which used DNA-protein cross-links as measure of exposure.

SOURCE: Adapted from EPA, 1991b.

DNA-protein cross-links as a measure of internal dose of formaldehyde (Heck et al., 1990). That work, initially conducted in rats, demonstrated a steep nonlinear relationship between formaldehyde concentration and formation of DNA-protein cross-links in nasal tissue, where most inhaled formaldehyde is deposited in rats. This suggested a correlation between such cross-links and tumors.

When the studies were extended to monkeys, a similar nonlinear relationship was observed between exposure concentration and DNA-protein cross-links in nasal tissue, but the concentration of DNA-protein cross-links per unit of exposure concentration was substantially lower than in the rat. Because the breathing patterns of humans more closely resemble those of monkeys than those of rats, the results of these studies suggested that using rats as a surrogate for humans might overestimate doses to humans, and hence the risk presented to humans by formaldehyde. EPA's most recent risk assessment (EPA, 1991e) used DNA-protein cross-links as the exposure indicator and estimated the human cancer risk (Table 6-2). EPA noted that the cross-links were being used only as a measure of delivered dose and that present knowledge was insufficient to ascribe a mechanistic role to the DNA-protein cross-links in the carcinogenic process.

The EPA risk estimates for formaldehyde have been the subject of extensive peer review and review by the SAB. The 1992 update was reviewed by the SAB Environmental Health Committee and Executive Committee. The SAB recommended that the agency attempt to develop an additional risk estimate using the epidemiological data and prepare a revised document reporting all the risk estimates developed by the alternative approaches with their associated uncertainties. The two examples just discussed used mechanistic data and modeling to improve the characterization of the exposure-dose link. It is possible that as knowledge increases, models can be developed that link dose to response; the possibility is further discussed in Chapter 7.

The same is true of the linearized multistage model. As noted earlier, this model assumes that risk is linear in dose. As noted earlier, however, rats exposed to formaldehyde show a steep nonlinear exposure-response relationship. This raises the possibility that the linearized multistage model might be inappropriate for at least some chemicals. It is possible that advances in knowledge of the molecular and cellular mechanisms of carcinogenesis will show a need to use other models either case by case or generically. More discussion of this matter can be found in Chapter 7.

The strategy advocated for formaldehyde would build on multistage models of the carcinogenic process that describe the accumulation of procarcinogenic mutations in target cells and the consequent malignant conversion of these cells (Figure 6-1). The Moolgavkar-Venzon-Knudson model substantially oversimplifies the carcinogenic process but provides structural framework for integrating and examining data on the role of DNA-protein cross-links, cell replication, and other biologic phenomena in formaldehyde-induced carcinogenesis (Moolgavkar

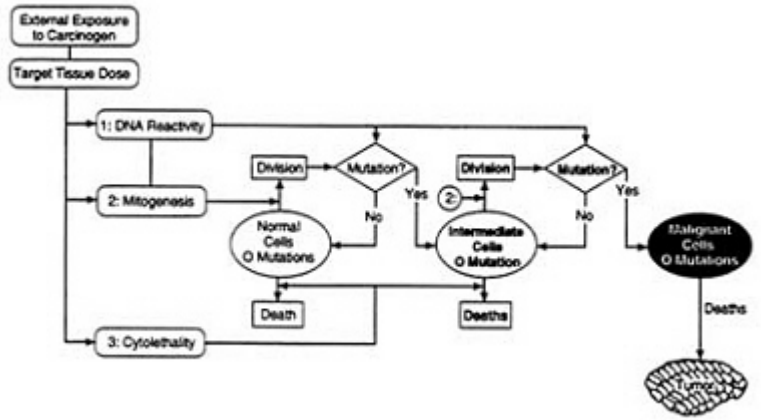


FIGURE 6-1 Model of chemical carcinogenesis built on multi-stage carcinogenesis model of Moolgavkar-Venzon-Knudson. SOURCE: Conolly et al., 1992. R eprinted with permission, copyright 1992 by Gordon & Breach, London.

and Venzon, 1979; Moolgavkar and Knudson, 1981; Moolgavkar et al., 1988; NRC, 1993b). Key features of this model are definition of the relationship of target-tissue dose to exposure and the use of that dose as a determinant of three outcomes: reactivity with DNA, mitogenic alterations, and cytolethality. These, in turn, cause further biologic effects: DNA reactivity leads to mutations, the mitogenic stimuli increase the rate of cell division, and cells die (cell death stimulates compensatory cell proliferation). Models like that shown provide a structured approach for integrating data on a toxicant, such as formaldehyde. It is anticipated that modeling will provide insight into the relative importance, at various exposure concentrations, of the two mechanisms that appear to have a dominant role in formaldehyde carcinogenesis: mutation and cell proliferation. Improved insight into their role could provide a mechanistic basis for selecting between the linearized multistage mathematical model now used for extrapolation from high to low doses and alternative models that might have more biologic plausibility.

Trichloroethylene

Trichloroethylene (TCE) is a chlorinated solvent that has been widely used in the industrial degreasing of metals. TCE is a concern to EPA as an air pollutant, a water pollutant, and a substance frequently present in ground water at Superfund sites. EPA carried out a risk assessment for TCE documented in a health assessment document (HAD) (EPA, 1985d) and a draft addendum incorporating

additional inhalation-bioassay data (EPA, 1987e). Both documents were reviewed by the SAB (EPA, 1984a; EPA, 1988j,k). The second document has not been issued in final form, and no further revision of EPA's risk assessment on TCE has been made since 1987.

The carcinogenic potency of TCE is based on the liver-tumor response in B6C3F1 mice, a strain particularly prone to liver tumors. The carcinogenicity of TCE might result from trichloroacetic acid (TCA), a metabolite of TCE that is itself known to cause liver tumors in mice. TCA is one of a number of chemicals that cause proliferation of peroxisomes, an intracellular organelle, in liver cells. Peroxisome proliferation has been proposed as a causal mechanism for the liver tumors, and proponents have asserted that such tumors should receive treatment in risk assessments different from evaluation under EPA's default assumptions. In particular, human liver cells might be much less sensitive than mouse liver cells to tumor formation from this mechanism, and the dose-response relationship might be nonlinear at low doses.

The SAB held a workshop in 1987 on peroxisome proliferation as part of its reviews on risk assessments for TCE and other chlorinated solvents. While endorsing a departure from the default on the alpha-2μ-globulin mechanism described in example 1 above, the SAB declined to endorse such a departure for peroxisome proliferation, noting that a causal relationship for this mechanism was "plausible but unproven." The SAB strongly encouraged further research, describing this mechanism for mouse liver tumors as "most promising for immediate application to risk assessment" (EPA, 1988k). The SAB criticized EPA on the draft Addendum on TCE (EPA, 1987e) for not adequately presenting uncertainties and for not seriously evaluating recent studies on the role of peroxisome proliferation (EPA, 1988*l*).

In the TCE case, departure from the defaults was rejected after an SAB review that recognized the peroxisome proliferation mechanism as plausible. Controversy over the interpretation of liver tumors in B6C3F1 mice continues. Some scientists assert that EPA's use of the tumor-response data from this particularly sensitive strain has been inappropriate (Abelson, 1993; ILSI, 1992). In the TCE example, departure from the defaults might become appropriate, on the basis of improved understanding of mouse liver tumors and their implications for human cancer. Although the SAB declined to endorse such a departure in 1987, it strongly encouraged further research as appropriate for supporting improved risk assessment.

Cadmium

Cadmium compounds are naturally present at trace levels in most environmental media, including air, water, soil, and food. Substantial additional amounts might result from human activities, including mining, electroplating, and disposal of municipal wastes. EPA produced an HAD on cadmium (EPA, 1981b) and

later an updated mutagenicity and carcinogenicity assessment (EPA, 1985e). The latter went through SAB review (EPA, 1984b), which pointed out many weaknesses and research needs for improving the risk assessment. No revision of the risk assessment on cadmium has occurred since 1985.

EPA used epidemiological data for developing a single unit risk estimate for all cadmium compounds. Use of the estimate from the best available bioassay would have given a unit risk for cadmium compounds higher by a factor of 50. The SAB and EPA in its response to SAB comments (EPA, 1985f) agreed that the solubility and bioavailability of different cadmium compounds were important in determining the risk associated with different cadmium compounds and that such differences might explain the discrepancy between the epidemiological data and the bioassay data. No implementation of the principle that cadmium compounds should be evaluated on the basis of bioavailability has yet been devised, although its importance to risk assessment for some air pollutants that contain cadmium is clearly set forth in EPA's response to the SAB (EPA, 1985f).

EPA's existing risk assessment for cadmium might be judged adequate for screening purposes. But the SAB review and the EPA response to it suggest that the carcinogenic risk associated with a specific cadmium compound could be overestimated or underestimated, because bioavailability has not been included in the risk assessment. A refined version of the risk assessment that includes bioavailability might be appropriate, especially if residual risks for cadmium compounds appear to be important under the Clean Air Act Amendments of 1990.

Nickel

Nickel compounds are found at detectable levels in air, water, food, and soil. Increased concentrations of airborne nickel result from mining and smelting and from combustion of fuel that contains nickel as a trace element. Nickel compounds present in smelters that use the pyrometallurgical refining process are clearly implicated as human carcinogens. EPA's HAD on nickel (EPA, 1986b) lists dust from such refineries and nickel subsulfide as category A (known human) carcinogens. A rare nickel compound, nickel carbonyl, is listed, on the basis of sufficient evidence in animals, as category B2. Other nickel compounds are not listed as carcinogens, although EPA states (EPA, 1986b, p. 2-11):

> The carcinogenic potential of other nickel compounds remains an important area for further investigation. Some biochemical and *in vitro* toxicological studies seem to indicate the nickel ion as a potentially carcinogenic form of nickel and nickel compounds. If this is true, all nickel compounds might be potentially carcinogenic with potency differences related to their ability to enter and to make the carcinogenic form of nickel available to a susceptible cell. However, at the present time, neither the bioavailability nor the carcinogenesis mechanism of nickel compounds is well understood.

The SAB reviewed the nickel HAD and concurred with EPA's listing of only the three rare nickel species as category A and B2 carcinogens (EPA, 1986c).

The results of bioassays on three nickel species by the National Toxicology Program are due to be released soon, and these results should provide a basis for revision of risk assessments for nickel compounds.

The cadmium and nickel examples point out an important additional default option: Which compounds should be listed as carcinogens when it is suspected that a class of chemical compounds is carcinogenic? Neither the cadmium risk assessment, the nickel risk assessment, or EPA's *Guidelines for Carcinogen Risk Assessment* (EPA, 1986a) provide specific guidance on this issue.

Dioxins

Dioxins is a commonly used name for a class of organochlorine compounds that can form as the result of the combustion or synthesis of hydrocarbons and chlorine-containing substances. One isomer, 2,3,7,8-tetrachlorodibenzo-*p*-diox-in (TCDD), is one of the most potent carcinogens ever tested in bioassays. EPA issued an HAD for dioxins (EPA, 1985g), which the SAB criticized for its treatment of the non-TCDD isomers that may contribute substantially to the overall toxicity of a mixture of dioxins (EPA, 1985h).

The potency calculation for TCDD has continued to be a subject of controversy. Research indicates that the toxic effects of TCDD may result from the binding of TCDD to the Ah (aromatic hydrocarbon) receptor. In 1988, EPA asked the SAB to review a proposal to revise its risk estimate for TCDD. SAB agreed with EPA's criticism of the linearized multistage model and its assessment of the promise of alternative models based on the receptor mechanism. But SAB did not agree that there was adequate scientific support for a change in the risk estimate. SAB carefully distinguished its recommendation from a change that EPA might wish to make as part of risk management (EPA, 1989f)

> The Panel thus concluded that at the present time the important new scientific information about 2,3,7,8-TCDD does not compel a change in the current assessment of the carcinogenic risk of 2,3,7,8-TCDD to humans. EPA may for policy reasons set a different risk-specific dose number for the cancer risk of 2,3,7,8-TCDD, but the Panel finds no scientific basis for such a change at this time. The Panel does not exclude the possibility that the actual risks of dioxin-induced cancer may be less than or greater than those currently estimated using a linear extrapolation approach.

A recent conference affirmed the scientific consensus on the receptor mechanism for TCDD, but there was not a consensus that this mechanism implied a basis for departure from low-dose linearity (Roberts, 1991). After the conference, and after the recommendations of the SAB (EPA, 1989f), EPA initiated a new study to reassess the risk for TCDD. That study is now in draft from and scheduled for SAB review in 1994.

The potencies of other dioxin isomers and isomers of a closely related chemical class, dibenzofurans, have been estimated by EPA with a toxic-equivalency-factor (TEF) method (EPA, 1986d). The TEF method was endorsed by the SAB as a reasonable *interim* approach in the absence of data on these other isomers (EPA, 1986e). The SAB urged additional research to collect such data. Municipal incinerator fly ash was used as an example of a mixture of isomers of regulatory importance that might be appropriate for long-term animal testing.

The EPA initiative for a review of TCDD is one of the few instances in which the agency has initiated revision of a carcinogen risk assessment on the basis of new scientific information. Dioxins and dibenzofurans are unique in that potency differences within this class of closely related chemical isomers are dealt with through a formal method that has undergone peer review by the SAB.

Example 3: Modeling Exposure-Response Relationship

If chemicals act like radiation at low exposures (doses) inducing cancer—i.e., if intake of even one molecule of a chemical has an associated probability for cancer induction that can be calculated—the appropriate model for relating exposure-response relationships is a linearized multistage model.

Of the 189 hazardous air pollutants, unit risk estimates are available for only 51: 38 with inhalation unit risks, which are applicable to airborne materials, and 13 with oral unit risks. The latter probably have less applicability to estimating the health risks associated with airborne materials. All 38 inhalation unit risk values have been derived with a linearized multistage model; i.e., it is assumed that the chemicals act like radiation. That might be an appropriate assumption for chemicals known to affect DNA directly in a manner analogous to that of radiation. For other chemicals—e.g., such nongenotoxic chemicals as chloroform—the assumption of a mode of action similar to that of radiation might be erroneous, and it would be appropriate to consider the use of biologically-based exposure-response models other than the linearized multistage model.

The process of choosing between alternative exposure-response models is difficult because the models cannot be validated directly for their applicability for estimating lifetime cancer risks at exposures of regulatory concern. Indeed, it is possible to obtain cancer incidence data on exposed laboratory animals and distinguish them from the control incidence only over a narrow range, from some value over 1% (10^{-2}) to about 50% (5×10^{-1}) cancer incidence. In regulation of chemicals, the extrapolation may be over a range of up to 4 orders of magnitude (from 10^{-2} to 10^{-6}), going from experimental observations to estimated risks of cancer incidence at exposures of regulatory concern. One approach to increasing the accuracy with which comparisons between measured outcome and model projections can be made involves increasing the size of the experimental populations. However, statistical considerations, the cost of studying large numbers of animals, and the greater difficulty of experimental control in

larger studies put narrow limitations on the use of this approach. Similar problems exist in conducting epidemiological studies.

An attractive alternative is to use advances in knowledge of the molecular and cellular mechanisms of carcinogenesis. Identification of events (e.g., cell proliferation) and markers (e.g., DNA adducts, suppressor genes, oncogenes, and gene products) associated with various steps in the multistep process of carcinogenesis creates a potential for modeling these events and products at low exposure. Direct tests of the validity of exposure-response models at risks of around 10^{-6} are not likely in the near future. However, with an order-of-magnitude improvement in sensitivity of detection of precancerous events with a probability of occurrence down to around 10^{-3}-10^{-2}, the opportunity will be available to evaluate alternative modes of action and related exposure-response models at substantially lower exposure concentrations than has been possible in the past. For example, it should soon be possible to evaluate compounds that are presumed to have different modes of action (direct interaction with DNA and genotoxicity versus cytotoxicity) and alternative models (linearized multistage versus nonthreshold) that might yield markedly different risks when extrapolated to realistic exposures and low risks.

Findings And Recommendations

Use of Default Options

FINDING: EPA's practice of using default options when there is doubt about the choice of appropriate models or theory is reasonable. EPA should have a means of filling the gap when scientific theory is not sufficiently advanced to ascertain the correct answer, e.g., in extrapolating from animal data to responses in humans.

RECOMMENDATION: EPA should continue to regard the use of default options as a reasonable way to cope with uncertainty about the choice of appropriate models or theory.

Articulation of Defaults

FINDING: EPA does not clearly articulate in its risk-assessment guidelines that a specific assumption is a default option.

RECOMMENDATION: EPA should clearly identify each use of a default option in future guidelines.

Justification for Defaults

FINDING: EPA does not fully explain in its guidelines the basis for each default option.

RECOMMENDATION: EPA should clearly state the scientific and policy basis for each default option.

Alternatives to Default Options

FINDING: EPA's practice appears to be to allow departure from a default option in a specific case when it ascertains that there is a consensus among knowledgeable scientists that the available scientific evidence justifies departure from the default option. EPA, though, has not articulated criteria for allowing departures.

RECOMMENDATION: The agency should consider attempting to give greater formality to its criteria for a departure, to give greater guidance to the public and to lessen the possibility of ad hoc, undocumented departures from default options that would undercut the scientific credibility of the agency's risk assessments. At the same time, the agency should be aware of the undesirability of having its guidelines evolve into inflexible rules.

Process For Departures

FINDING: EPA has relied on its Science Advisory Board and other expert bodies to determine when a consensus among knowledgeable scientists exists.

RECOMMENDATION: EPA should continue to use the Science Advisory Board and other expert bodies. In particular, the agency should continue to make the greatest possible use of peer review, workshops, and other devices to ensure broad peer and scientific participation to guarantee that its risk-assessment decisions will have access to the best science available through a process that allows full public discussion and peer participation by the scientific community,

Missing Defaults

FINDING: EPA has not stated all the default options in each step in the risk-assessment process, nor the steps used when there is no default. Chapters 7 and 10 elaborate on this matter and identify several possible "missing defaults."

RECOMMENDATION: EPA should explicitly identify each generic default option in the risk-assessment process.

7

Models, Methods, and Data

Introduction

Health risk assessment is a multifaceted process that relies on an assortment of methods, data, and models. The overall accuracy of a risk assessment hinges on the validity of the various methods and models chosen, which in turn are governed by the scope and quality of data. The degree of confidence that one can place in a risk assessment depends on the reliability of the models chosen and their input parameters (i.e., variables) and on how well the boundaries of uncertainty have been quantified for the input parameters, for the models as a whole, and for the entire risk-assessment process.

Quantitative assessment of data quality, verification of method, and validation of model performance are paramount for securing confidence in their use in risk assessment. Before a data base is used, the validity of its use must be established for its intended application. Such validation generally encompasses both the characterization and documentation of data quality and the procedures used to develop the data. Some characteristics of data quality are overall robustness, the scope of coverage, spatial and temporal representativeness, and the quality-control and quality-assurance protocols implemented during data collection. More specific considerations include the definition and display of the accuracy and precision of measurements, the treatment of missing information, and the identification and analysis of outliers. Those and similar issues are critical in delineating the scope and limitations of a data set for an intended application.

The performance of methods and models, like that of data bases, must be characterized and verified to establish their credibility. Evaluation and validation

procedures for a model might include sensitivity testing to identify the parameters having the greatest influence on the output values and assessment of its accuracy, precision, and predictive power. Validation of a model also requires an appropriate data base.

This chapter discusses the evaluation and validation of data and models used in risk assessment. In cases where there has been an insufficient assessment of performance or quality, research recommendations are made. Although in this chapter we consider validation issues sequentially, according to each of the stages in the (modified) Red Book paradigm, our goal here is to make the assessment of data and model quality an iterative, interactive component of the entire risk-assessment and risk-characterization process.

Emission Characterization

As described in Chapter 3, emissions are characterized on the basis of emission factors, material balance, engineering calculations, established Environmental Protection Agency (EPA) protocols, and measurement. In each case, this characterization takes the structural forms of a linearly additive process (i.e., emissions equals product – [feedstock + accumulations]), a multiplicative model (i.e., emissions equals [emission factor][process rate]), or an exponential relationship (e.g., emission equals intercept + [(emission factor) (measurement) ^{exp}]).

The additive form is based on the mass-balance concept. An estimate is made by measuring the feedstock and product to determine an equipment-specific or process-specific transfer coefficient. This coefficient is used to estimate emissions to the atmosphere. The measurements available for the additive form are often not sufficiently precise and accurate to yield complete information on inputs and outputs (NRC, 1990a). For example, an NRC committee (NRC, 1990a) considered a plant that produced 5 million pounds of ethylene per day and used more than 200 monitoring points to report production with a measurement accuracy of 1%, equivalent to 50,000 lb of ethylene per day. The uncertainty in this estimate (50,000 lb) greatly exceeded a separate estimate of emissions, 191 lb, which was calculated by the plant and was confirmed by monitoring of the emission points. Thus, despite the apparently good precision of estimates within 1%, the additive method was not reliable. This seems to be generally true for complicated processes or multiple processing steps.

The other forms are based on exponential and multiplicative models. Each may be deterministic or stochastic. For example, emissions from a well-defined sample of similar sources may be tested to develop an emission factor that is meant to be representative of the whole population of sources. A general difficulty with such fits that use these functional (linear or one of several nonlinear forms) forms is that the choice of form may be critical but hard to validate. In addition, it must be assumed that data from the sources used in the calculations are directly applicable to the sources tested in process design and in the management

and maintenance approaches of the organizations that run them are the same in all cases.

An example of an exponential form of an emission calculation is shown in Figure 7-1. This figure shows the correlation between screening value (the measurement) and leak rate (the emission rate) for fugitive emissions from a valve. The screening value is determined by measuring the hydrocarbons emitted by a piece of equipment (in this case, a valve in gas service) with an instrument like an OVA (organic-vapor analyzer). The leak rate (i.e., emission) is then determined by reading the value on the y axis corresponding to that screening value. Note that the plot is on a log-log scale, so that a "3" on the x axis indicates that a 1,000-ppm screening value corresponds to a "-3.4" on the y axis, or 0.001 lb/hr for each value in gas service at that screening value. The observations here are based on an analysis conducted for 24 synthetic organic chemical manufacturing industry (SOCMI) units representing a cross-section of this industry (EPA, 1981a).

As part of this analysis, a six-unit maintenance study (EPA, 1981a) was used to determine the impact of equipment monitoring and maintenance using an OVA instrument on emission reduction. The equation derived for the value

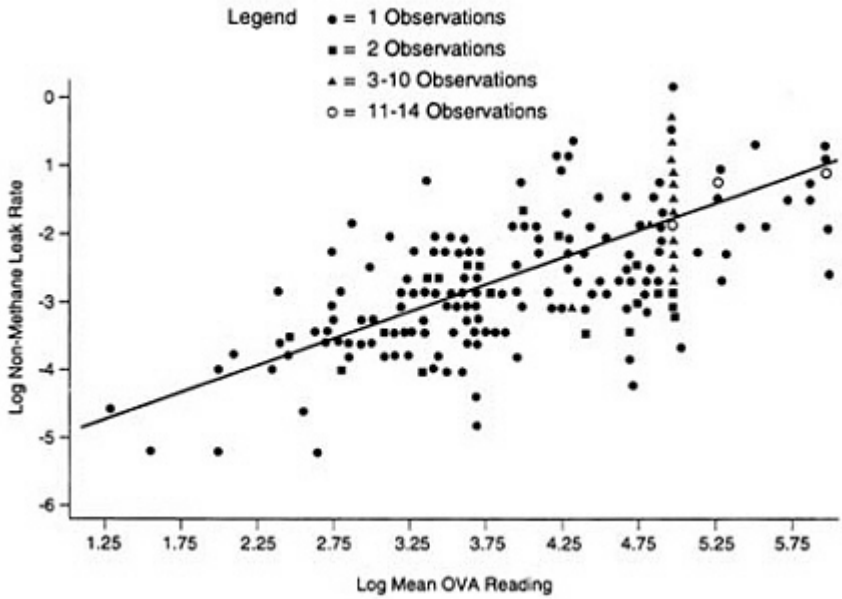


FIGURE 7-1 Log_{10} leak rate vs. log_{10} OVA reading for values-gas service. SOURCE: EPA, 1981a.

emissions in gas service explains only 44% (square of the correlation coefficient) of the variance in the points shown in Figure 7-1. Similar results were obtained from other possible emission points.

The facilities in this SOCMI study could reduce the estimate of their emissions by 29-99% by determining plant-specific emission factors, indicating the difficulties in using industry-wide average to represent specific plant behavior.

The multiplicative form improves on the emission-factor approach, in that it incorporates more features of the process, attempting to accommodate the types of equipment being used, the physical properties of the chemical, and the activity of the equipment as a whole. The deterministic form of the multiplicative model is based on the chemical and physical laws that determine the emission rate. The variables measured—vapor pressure, molecular weight, temperature, etc.—are chemical physical properties that are related to the emission rate. The multiplicative form provides some scientific basis for the estimate beyond the simple curve-fitting. However, it has difficulties, because some of the properties are not constant. For example, the ambient air temperature, one factor in determining the emission rate, can vary quite widely within a day. The average temperature for a given period, such as a month, is used for ease in calculation, but this practice introduces some error. EPA might want to consider a more detailed analysis in which the emissions that occur during the period are stratified into groups with smaller variations in variables such as ambient temperature. The emissions in the strata could be estimated and weighted sums calculated to provide a better estimate.

Probably the most accurate procedure is to use none of those "forms" to determine emissions, but rather to sample stack and vent emissions at each source. However, such sampling can be quite expensive, and the costs could overburden owners of small sources. Apart from costs, the primary difficulty with this procedure is that it yields an estimate for one site on one occasion. Emissions could change because of a variety of factors. An alternative to testing is to estimate emissions from monitoring data. Continuous emission monitors (CEMs), which are available for a small number of chemicals, are placed in stacks or near fugitive-emission points to measure the concentration of a chemical being released; concentrations can then be converted to amounts. However, CEMs can be expensive and difficult to maintain, and they may produce incomplete or inaccurate measurements. When such testing is conducted, however, they may show that other kinds of estimates are seriously in error. For example, a study (Amoco/EPA, 1992) compared emissions estimated primarily from emission factors with those determined during testing. The measured overall actual estimate of emissions was more than twice as high as the TRI estimate for a variety of reasons, including identification of new sources, overestimation or underestimation of the importance of some sources, and the lack of a requirement to report source emissions under a particular regulation.

Evaluation of EPA Practice EPA has worked diligently to help members of the public who are required to provide emission estimates for regulatory purposes. This 20-year effort has provided documents that are used to estimate air-pollutant emissions throughout the world. However, in some cases, EPA has had to provide emission estimation factors based on very little information about the process involved; it was difficult to check the assumption that the process for which the calculation is being used is similar to the process that was tested in the development of the emission factor.

There are two basic difficulties with the way EPA applies its emission estimation techniques. First, most estimates are made by using the emission factors or by fitting the linear or exponential forms. As discussed previously, the accuracy of emission estimates using these techniques might not be high.

Second, the information is generated in such a way that only point estimates are presented. Although it is clear from the earlier discussion that there can be uncertainty in the estimates, EPA has extensive files on how the emission factors were determined, and this information presumably contains enough points to generate distribution of emissions rather than just a point estimate. EPA provides only qualitative ratings of the accuracy of the emission method. The ratings are not based on the variance in the estimate, but just on the number of emission points used to generate the data. If there are enough points to generate an emission factor, it is possible to estimate the distribution of emission factors from which an estimate can be chosen to solve a particular exposure-risk estimation problem.

However, the emission factors are given only a "grade" from A (best) to E relative to the quality and amount of data on which estimates are based. An emission factor based on 10 or more plants would likely get an "A" grade, whereas a factor based on a single observation of questionable quality or one extrapolated from another factor for a similar process would probably get a D or E. The grades are subjective and do not consider the variance in the data used to calculate factors. According to EPA (1988e), the grades should "be used only as approximations, to infer error bounds or confidence intervals about each emission factor. At most, a [grade] should be considered an indicator of the accuracy and precision of a given factor used to estimate emissions from a large number of sources." The uncertainty in the estimates is such that EPA is not comfortable with the A-E system and is developing a new qualitative system to indicate uncertainty. EPA is attempting to generate estimation factors for hazardous air pollutants industry by industry, but it is still hesitant to ascribe any sort of uncertainty to emission factors.

A single disruption in operation of a plant can increase the release rate for some interval (hour or day). An extreme example is the dioxin release from a manufacturing plant in Seveso, Italy. Such disruptions are not incorporated into any of the emission characterizations, except for the few cases where emission monitoring is available. However, in those cases, emissions might be so high

that they exceed the maximum reading of a monitor and thereby lead to just a lower bound (if this problem is recognized) or even to a serious underestimate of the actual emission. Furthermore, the frequency and duration of such episodes are unpredictable.

Therefore, EPA should also attempt to make some sort of quantitative estimates of the variability of measured emissions among sources within a category and of the uncertainty in its overall emission estimates for individual sources and the source category as a whole. This issue is discussed in more depth in Chapter 10, but could involve analyzing the four kinds of circumstances as appropriate for a particular source type—routine, regular maintenance, upsets and breakdowns, and rare catastrophic failures. EPA could also note the implications of the dynamics of causation of different effects for emission estimation, and the resulting need for estimates of exposure and exposure variability over different averaging times.

The itemization of emissions by chemical constituent also raises problems. Emission characterization methods often provide only the amount of VOCs (volatile organic compounds) that is emitted. The amounts of particular compounds (benzene, toluene, xylene, etc.) within these VOC emissions are often not individually reported. Without the emission data on particular compounds, it is impossible to provide the information needed for exposure modeling in the risk-assessment process.

EPA does not appear to be making major strides toward improving the methods used to evaluate emissions. Although EPA is making extensive efforts to distribute the emission factors it has generated, the committee has found insufficient effort either to evaluate the accuracy of the underlying method used to derive the emission estimates or to portray the uncertainty in the emission factors. The primary exception is a joint effort of the Chemical Manufacturers Association (CMA) and EPA on fugitive emissions called Plant Organization Software System for Emission Estimation or POSSEE (CMA, 1989). In this case, companies are testing fugitive emissions within plants and collecting data on chemical and physical variables to derive emission estimates based on deterministic models (which use physical and chemical properties), rather than stochastic models. There have been efforts to increase the scientific justification of estimates of emissions from storage tanks: the American Petroleum Institute has developed data that have been used for developing the estimation method shown in the multiplicative form described above. The question then arises as to how to approach emission estimates in exposure assessments and risk assessments. The uncertainty in the mass-balance approach (additive form) can be so large that its use should be discouraged for any purposes other than for a very general screening. It is unlikely that an emission estimate derived with this method would be appropriate for risk assessment.

The linear emission-factor approach could be used as a general screening tool in an exposure assessment. As indicated by EPA in response to a question from this committee:

> While emission factor-based estimates can be useful in providing a general picture of emissions across an entire industrial category, use of such factors to provide inputs to a site-specific risk assessment may introduce a great deal of uncertainty into that assessment.

If such an approach is used for an entire industrial category, then at least the uncertainty of each emission factor should be determined. If there is enough information to derive an emission factor, then a probability distribution could be calculated. There may then be disagreement about where on the probability distribution the emission estimate should be chosen. However, it is better to make the choice explicitly, as discussed in Chapter 9. The same situation is true for emissions estimated with the exponential and multiplicative approaches. EPA should include a probability distribution in all its emission estimates.

One method to determine the uncertainty in an emission estimate more easily would be to require each person submitting an emission estimate (for SARA 313 requirements, permitting, etc.) to include an evaluation of the uncertainty in the estimate. EPA could then evaluate the uncertainty in the estimation methods to determine whether the estimation was done properly. Although that might increase the costs of developing submissions slightly, the organization submitting the estimate might benefit from the results. Small sources unable to afford such analysis could instead define a range that is consistent with known or readily determined factors in their operation (e.g., for a dry cleaner, the pounds of clothes per week and gallons of solvent purchased each month).

EPA is reviewing, revising, and developing emission estimation methods for sources of the 189 chemicals. It is focusing on adding data, rather than evaluating its basic approach—the use of a descriptive model, instead of a model based on processes, for emission estimation. It appears from the examples given above that the uncertainties in emissions can dominate an exposure assessment and that a concerted effort to improve emission estimation could serve to substantially reduce the uncertainty in many risk estimates. Combined industry efforts to improve the techniques used to estimate fugitive emissions on the basis of physical and chemical properties (not just curve-fitting) should be encouraged.

Exposure Assessment

Once an emission characterization is developed, it becomes one of the inputs into an air-quality model to determine the amount of a pollutant in ambient air at a given location. A population-exposure model is then used to determine how much of a pollutant reaches people at that location.

Population

The size of the population that might be exposed to an emission must be determined. Population data have been collected, published, and scrutinized for

centuries. Many such data refer to entire populations or subpopulations, so questions of representation and statistical aspects of sampling do not arise in their usual form. Even where sampling is used, a large background of technique and experience allows complex estimation and other kinds of modeling to proceed without the large uncertainties inherent in, for example, extrapolation from high to low doses of toxic agents or from rodents to humans.

Population data are almost always affected to some degree by nonsampling error (bias), but this is well categorized, understood, and not a serious problem in the context of risk assessment. For example, terminal-digit preference (e.g., a tendency to report ages that end in zero or five) has been minimal since the attainment of nearly universal literacy and especially since the adoption of birth certification. Attainment of advanced ages (i.e., over 80 years) is still overstated, but this is not quantitatively serious in age estimation for purposes of risk assessment (because EPA still assumes that 70 years is the upper-bound value of the length of a liftime). Population undercounts in the U.S. census of 1990 averaged about 2.1% and were substantially higher for some subgroups, perhaps up to 30%; however, even 30% uncertainty is smaller than many other sources of error that are encountered in risk assessment. The largest proportionate claim of uncertainty seems to be in the number of homeless persons in the United States; estimated uncertainty is less than a factor of 10.

Estimation of characteristics in groups or subgroups not examined directly is subject to additional uncertainty. For example, the 1992 population is not directly counted, but standard techniques are used to extrapolate from the census of 1990, which was a nearly complete counting of the population. Investigators have found earlier years estimates to be generally quite accurate, whether the extrapolations were strictly mathematical (e.g., based on linear extrapolation) or demographic (based on accounting for the addition of 3 years between 1990 and 1993, with adjustments for deaths, for births of the population under age 3, deaths, and net migration). The problems are greater for states and smaller areas, because data on migration (including internal migration) are not generally available.

Error tends to increase as subgroups get smaller, partly because statistical variability increases (i.e., small sample size leads to less precision in the estimate of the central tendency with any distributed measurement), but also because individual small segments are not as well characterized and as well understood as larger aggregates and because population data are generally collected according to a single nationwide protocol that allows for little deviation to accommodate special problems.

The committee is comfortable about using published population data for nearly all population characteristics and subgroups. Where adjustment to reduce errors is feasible, it should be used; but in the overall context of risk assessment, error in population assessment contributes little to uncertainty.

In some cases, a research study must define and identify its own population

without help from official census and surveys. An example is a long-term followup study of workers employed in a specific manufacturing plant. When such studies are done by skilled epidemiologists, total counts, ages, and other demographic items tend to be accurate to within a factor of 2 or 3. The largest uncertainties are likely to be in the estimation of exposure to some toxic agent; these are often dealt with by the use of rough categories (high, medium, and low exposure) or surrogate measures (e.g., years employed in a plant, rather than magnitude of exposure). Errors in such work are of great concern, but they tend to be peculiar to each study and hence lead to study-specific remedies in design, performance, or analysis. They tend to be smaller than other kinds of uncertainties, but can still be of concern if a putative effect is also small.

As indicated, population data derived from a census and fortified with estimation methods are regarded as accurate and valid, and uncertainties introduced into risk assessment are relatively small. There is a need, however, for information on additional population characteristics that are not included in the census. There is a paucity of activity-pattern information, and population-exposure models or individual-exposure-personal-exposure models have not been adequately tested or validated, because they use people's activity to estimate exposure to chemicals in air. Only a few small efforts have been undertaken to develop such a data base, namely, EPA's Total Exposure and Assessment Methodology (TEAM) program and the California EPA's State Activity Pattern Study. Those programs have acquired information about people's activities that cause the emission of air pollutants or place people in microenvironments containing air pollutants that potentially lead to exposure. There is a need to develop a national data base on activity patterns that can be used to validate models that estimate personal exposure to airborne toxic chemicals. Accurately described activity patterns coupled with demographic characteristics (e.g., socioeconomic) can be used for making a risk assessment and assessing the environmental equity of risk across socioeconomic groups and races.

When exposure-characterization models are developed for use in risk assessment, the bias and uncertainty that they yield in the calculation of exposure estimates should be clearly defined and stated, regardless of whether activity patterns are included. Later, the choice of an appropriate model from an array of possibilities should be based on, but not necessarily limited to, its quantitative measure of performance and its rationale should be included with a statement of the criteria for its selection.

Air-Quality Model Evaluation

Air-quality models are powerful tools for relating pollutant emissions to ambient air quality. Most air-quality models used in assessing exposure to toxic air pollutants have been extensively evaluated with specific data sets, and their underlying mathematical formulations have been critically reviewed. Relative

to some of the other models for risk assessment of air pollutants, air-quality models probably enjoy the longest history of model evaluation, refinement, and re-evaluation. For example, the original Gaussian-plume models were formulated and tested in the 1950s. That does not mean, however, that model evaluation does not still continue or that the model evaluation should be dismissed in assessing air-pollutant exposure; in fact, previous studies have shown the benefits of model evaluation in every application.

Evaluation of the air-quality models and other components of air-pollutant risk assessment is intended to determine accuracy for providing the details required in a given application and to provide confidence in the results. In air-quality modeling, that is particularly important. A Gaussian-plume model, when used with the input data generally available, might not correctly predict where maximal concentrations will be realized (e.g., because winds at the nearest station, such as an airport, might differ in direction from winds near the source of interest), but should provide a reasonable estimate of the distribution of pollutant concentrations around the site. That might be sufficient for some applications, but not others. Model evaluation can also add insight as to whether a tool is "conservative" or the opposite, and it can provide a quantitative estimate of uncertainty.

Of particular concern are the more demanding applications of models, such as in areas of complex terrain (e.g., hills, valleys, mountains, and over water), when deposition is important, and when atmospheric transformation occurs. As discussed below, it is difficult enough to use models in the simple situations for which they were specifically designed. One should always try to ascertain the level of accuracy that can be expected from a given model in a given application. Sufficient studies have been performed on most air-quality models to address that question.

Zannetti (1990) reviews evaluations of many air-quality models, including Gaussian-plume models. Evaluation procedures have recently been reviewed for photochemical air-quality models (NRC, 1991a). Similar procedures are applicable to other models. In essence, the models should be pushed to their limits, to define the range in which potential errors in either the models themselves or their inputs still lead to acceptable model performances and so that compensatory errors in the models and their inputs (e.g., meteorology, emissions, population distributions, routes of exposure, etc.) will be identified. That should lead to a quantitative assessment of model uncertainties and key weaknesses. As pointed out in the NRC (1991a) report, model evaluation includes evaluation of input data. The greatest limitation in many cases is in the availability and integrity of the input data; for the most part, many models can give acceptable results when good-quality input data are available.

A key motivation in model evaluation is to achieve a high degree of confidence in the eventual risk assessment. Pollutant-transport model evaluation, as it pertains to estimating air-pollutant emissions, has been somewhat neglected and

is used without adequate discussion and analysis. For example, the modeling of emissions from the ASARCO smelter (EPA, 1985b) showed significant bias. However, the reasons for both the bias and errors were not fully identified. A major plume-model validation study was mounted in the early 1980s with support of the Electric Power Research Institute (EPRI); it was the first study of a large coal-fired power plant situated in relatively simple terrain. The study compared three Gaussian-plume models and three first-order closure numerical (stochastic) models, and an experimental, second-order closure model, for which ground-level concentrations were obtained with both routine and intensive measurement programs (Bowne and Londergan, 1983). (*First-order closure* and *second-order closure* refer to how the effects of turbulence are treated.) The authors conclude that

- The models were poor in predicting the magnitude or location of concentration patterns for a given event.
- The models performed unevenly in estimating peak concentrations as a function of averaging time; none provided good agreement for 1-, 3-, and 24-hour averaging periods.
- The cumulative distribution of hourly concentrations predicted by the models did not match the observed distribution over the full range of concentration values.
- The variation of peak concentration values with atmospheric stability and distance predicted by the Gaussian models did not match the pattern of observed peak values.
- One of the first-order closure models performed better than the Gaussian models in estimating peak concentration as a function of meteorological characteristics, but its predictive capacity was poorer than desirable for detailed risk assessments, and it systematically overpredicted the distance to the maximal concentrations.
- One of the other first-order closure models systematically underpredicted plume impacts, but its predictive capacity was otherwise superior to that of the Gaussian models.
- An experimental second-order closure model did not provide better estimates of ground-level concentrations than the operational models.

Predictions and observed pollutant concentrations often differed by factors of 2-10. It is clear from the study—in which there was no effect of complex terrain, heat islands, or other complicating effects—that the dispersion models had serious deficiencies. Dispersion models have been developed since then, but they require further development and improvement and they warrant evaluation when applied to new locations or periods.

Larger-scale urban air-quality models perform better in predicting concentrations of secondary species—such as ozone, nitrogen dioxide, and formaldehyde—even though the complex chemical reactions might seem to make the task

harder. Prediction accuracy, on the average, is usually within about 10% (NRC, 1990a). This performance is due in part to the coarser spatial resolution used by the model, the chemical transformation times allowing the dispersion from the original sources, and better spatial separation of the sources. The lower spatial resolution, with increased chemical detail and performance, leads back to a consideration of model choice and evaluation: What type of detail is required from a particular model application and what level of performance can be expected?

In summary, model evaluation is an integral part of any risk assessment and is crucial for providing confidence in models. Evaluation procedures have been developed for various classes of air-quality models. Studies have shown that air-quality models can give reasonable predictions, but do not always (or often) do so. Results of a model evaluation can be used in an uncertainty analysis of predicted risk.

Evaluation of EPA Practice The validity of the population-exposure models used by EPA remains largely untested. Ott et al. (1988) used data from EPA's TEAM studies of carbon monoxide (CO) of Denver and Washington, D.C., to examine the validity of the SHAPE model and compared the estimated co-exposure distribution based on the SHAPE model with the distribution based on direct measurement (personal monitoring). They found the estimated average exposure to be similar with the two approaches, but the ranges in estimated exposure distributions were quite different. The SHAPE exposure model predicted median values well, but there were substantial discrepancies in the tails of the distribution.

Duan (1991) also using data from EPA's TEAM study of carbon monoxide in Washington, D.C., found that the concentrations and time intervals were independent and tested the effectiveness of a "variance-components exposure" model in comparison with SHAPE. Both the long-term average concentrations and short-term fluctuations in concentration were important in predicting exposure. Duan (1988) and Thomas (1988) examined several statistical parameters for several microenvironments and found the time-invariant component (i.e., a component that does not vary with time, often taken as a background level) to be dominant. Thus, there has been some effort to validate the exposure models developed for research purposes.

There have been no systematic attempts, however, to validate either of the exposure models used for regulatory purposes, the Human Exposure Model (HEM) and the National Ambient Air Quality Standard Exposure Model (NEM). The dispersion-model portion of HEM was compared with other simple Gaussian-plume models, and the results were similar. However, neither actual airborne concentrations nor measured integrated exposures to any airborne constituent were compared with the model results to test its utility in estimating individual or population exposures. Comparison of the site-specific model used to evaluate the health impact of arsenic from the ASARCO smelter in Tacoma,

Washington, from the few available data proved to have low marginal accuracy, and arsenic in the exposed human urine samples did not correlate well with estimated exposures, as discussed in Chapter 3. Thus, the effectiveness of these models is essentially unknown, although it will be important to understand their strengths and limitations, including prediction accuracy and the associated uncertainty, when residual risk must be estimated after installation of Maximum Achievable Control Technology (MACT).

When EPA conducts a risk assessment of a hazardous air pollutant, it generally relies on Gaussian-plume models. Gaussian-plume models are inadequately formulated, so inaccuracies appear in predicted pollutant concentrations (e.g., Gaussian-plume models generally are not applicable for nonlinear chemistry or particle dynamics). Furthermore, the inputs to these models are often inaccurate and not directly appropriate for a given application. In practice, application of Gaussian-plume models has not been adequately evaluated, and some evaluations have shown substantial discrepancies. More comprehensive and robust pollutant-transport models (i.e., those more directly applicable to a wider variety of situations) are available, including stochastic Lagrangian and photochemical models, and evaluations have shown good agreement with direct observations. In specific applications, model evaluation (via pollutant monitoring and assessment of model inputs and theory) should be undertaken and ranges of applicability determined. Demonstrations should include, but not be restricted to, showing that the model assumptions reasonably represent physical-chemical behavior of the contaminant, source configuration, and atmospheric dispersion. For environmental conditions for which the performance of Gaussian-plume models are demonstrated to be unsatisfactory, more comprehensive models should be considered; however, their superior performance should be documented and clearly evident when they are considered as an alternative in a risk assessment.

EPA has generally not included population activity, mobility, and demographics and has not adequately evaluated the use of population averages (as used by default in HEM) in its exposure assessments. Exposure models, such as NEM and SHAPE, have been developed to account for personal activity. Population-activity models should be used in exposure assessments; however, their accuracy should be clearly demonstrated before considering them as alternatives to the default approach. Demographics might also play a role in determining risk. Further evaluation of some simple methods (e.g., use of population centroids), compared with more comprehensive tools (e.g., NEM and SHAPE), is warranted, before they are considered in lieu of the default option.

EPA currently uses HEM to screen exposure associated with HAP releases from stationary sources. The HEM-II model uses a standardized EPA Gaussian-plume dispersion model and assumes nonmobile populations residing outdoors at specific locations. The HEM construct is not designed to provide accurate estimates of exposure in specific locations and for specific sources and contaminants when conditions are not represented by the simplified exposure- and dispersion-model

assumptions inherent in the standard HEM components. Alternative models for transport and for personal activity and mobility can be adopted in an exposure-modeling system to provide more accurate, scientifically founded, and robust estimates of pollutant-exposure distributions (including variability, uncertainty, and demographic information). Those models can be linked to geographic data bases to provide both geographic and demographic information for exposure-modeling systems.

Application of HEM generally does not include noninhalation exposures to hazardous air pollutants (HAPs) (e.g., dermal exposure), but these routes can be important. Modeling systems similar to extensions of HEM have been developed to account for the other pathways. Unless there is good evidence to the contrary, the contribution of alternative pathways of exposure to HAPs should be considered explicitly and quantified in a risk assessment.

Relatively simple models for exposure assessments, such as HEM, can provide valuable information for setting priorities and determining what additional data should be developed. However, exposure estimates that use this model can have large uncertainties (e.g., a factor of 2-10 due to the Gaussian-plume dispersion model used in HEM alone). Furthermore, Gaussian-plume models, in general, have not been validated for pollutants that are reactive and easily transformed to other chemicals such as organic gases (e.g., formaldehyde), particles, and acids (e.g., nitric and sulfuric acids). Multiple exposure routes can add still more uncertainty as to actual exposure. Uncertainty can be used as a tool for assessing the performance of a model like HEM. This is because HEM is based on very simplified descriptions of pollutant dynamics and was designed for use as a screening tool for estimating human exposure via inhalation.

The predictive accuracy and uncertainty associated with the use of the HEM should be clearly stated with each exposure assessment. The underlying assumption that the calculated exposure estimate is a conservative one should be reaffirmed; if not, alternative models whose performance has been demonstrated to be superior should be used in exposure assessment.

Assessment Of Toxicity

The first step in assessing human toxicity based on animal experiments is the extrapolation of observations from studies in rats, mice, monkeys, and other laboratory animals to humans. The extrapolation procedure used in risk assessment to assess the toxicity of a substance is both an intellectual exercise and a tool for making practical decisions. It is based on two assumptions: that the biological response to an external stimulus in one species will occur in a different species that is subjected to the same stimulus and that the biological response is proportional to the size of the stimulus (except that a very small stimulus will often result in only a transient response or no immediate response at all). Those two assumptions are invoked whenever extrapolation from animals to humans

and from high doses to low doses is performed. Cancer and other end points are discussed separately here because considerations related to extrapolation can differ.

Cancer

Qualitative Considerations

Cancer, defined as abnormal and uncontrolled growth, is ubiquitous among higher organisms; it occurs in plants, animals, and humans. In some cases, carcinogens can be identified as physical or chemical agents or self-replicating infectious agents. Many epidemiological studies have documented an association between exposure to particular chemicals and an increased incidence of particular malignancies in humans (Doll and Peto, 1981). Examples are cancers related to exposure to industrial agents—such as aniline dyes, mustard gas, some metal compounds, and vinyl chloride—and, in the general population, tobacco and tobacco smoke. Perhaps most convincing in this context is the repeated observation that cessation of exposure to a given chemical (e.g., cessation of smoking or introduction of appropriate mitigation or hygienic measures) results in a decrease in cancer incidence. When tested in animal studies, almost all known human carcinogens have been found to produce cancer in other mammals. There are a few exceptions to that rule, e.g. tobacco smoke in laboratory animals. Recent advances in the understanding of basic mechanisms of carcinogenesis, often very similar in laboratory animals and humans, lend credibility to a relationship between animal carcinogenesis and human carcinogenesis, particularly when mutagenicity is involved (OSTP, 1985; Barbacid, 1986; Bishop, 1987); in other cases, advances in the understanding of species-specific mechanisms of carcinogenesis do not support a relationship between humans and specific laboratory animals studied to date (Ellwein and Cohen, 1992). Current long-term carcinogenicity bioassays are conducted with rodents using, among other doses, the highest dose that does not reduce survival as a result of causes other than cancer, known as the maximum tolerated dose (MTD). Information acquired from rodent bioassays conducted at the MTD might yield information on whether a chemical can produce tumors in humans, but it generally cannot provide information on whether it produces tumors through generalized, indirect mechanisms or directly as a result of its specific properties. Mechanistic data could resolve the question of whether it is valid to extrapolate the results of a bioassay to humans (see NRC, 1993b). Current regulatory practice takes the view that in the absence of information to the contrary, animal carcinogens are human carcinogens; however, the data base supporting this assumption is not complete.

Obtaining more information on the biological mechanisms of carcinogenesis, their dose dependence, and their interspecies relevance will permit better and

more valid qualitative and quantitative extrapolations. For example, there is a tendency to give more weight to an observation when it relates chemical exposure to development of malignant tumors and to place less emphasis on an observation that suggests that a given chemical induces benign tumors. It might be an oversimplification to consider one category of abnormal growth as invariably detrimental and another as comparatively harmless. Tumor biology is much more complicated. Most, if not all, bronchial adenocarcinomas will kill when they run their course, whereas subcutaneous lipomas will not; however, excision of a malignant basal cell skin tumor is considered a cure, whereas a benign tumor of the VIIIth cranial nerve or of the pituitary gland can be lethal. Available knowledge on causes of cancer and on the biological behavior of tumors does not permit us to ascertain whether a compound that produces a benign tumor in laboratory animals would be either capable or incapable of producing a malignant tumor in humans. In the absence of information to the contrary, the conservative view equates abnormal growth with carcinogenicity. Circumstances that produce benign tumors in animal systems might have the potential for producing abnormal growth in humans, depending on the mechanism involved. Many benign tumors are most easily produced in animal strains that already have an inherently high spontaneous incidence of such tumors (e.g., liver and lung adenomas in mice and mammary tumors in rats). Studies of the genetic, biochemical, hormonal, and other factors that determine development of such tumors might improve the validity of human risk assessments based on animal studies, and should be pursued more vigorously.

The assumption that the organ or tissue affected by a chemical in animals is also the site of greatest risk in humans should also be made cautiously. It is likely that the site of tumor formation is related to the route of exposure and to numerous pharmacokinetic and pharmacodynamic factors. Each route of exposure might result in carcinogenicity and should be considered separately. It probably is reasonable to assume that in some cases, animal models of carcinogenesis can be used to predict the development of human tumors at specific sites, provided that conditions of exposure are comparable. However, if exposure conditions are not similar, that might not be true. For example, it might well be incorrect to assume that agents that produce sarcomas in laboratory animals after subcutaneous injection will induce sarcomas in humans after inhalation. Animal models can be used to detect potential carcinogenicity; however, extrapolating from animal models to particular human organs is not valid without a great deal of additional mechanistic information, such as information on the effects of exposure route, dose, and many other factors, including the metabolism of the agent in question.

Evaluation of EPA Practice Experience has shown that, in a broad sense, extrapolation from species to species is justifiable (Allen et al., 1988; Crump, 1989; Dedrick and Morrison, 1992). It is prudent to assume that agents that

cause abnormal growth of tissue components in laboratory animals will do so in humans. The animal species (mice and rats) most commonly used in the National Toxicology Program (NTP) to make predictions about human carcinogenesis were selected for convenience, not because they have been demonstrated to predict human risks accurately. For example, the risk of inhaled particles for humans might be underestimated in animal assays that use rats and mice, which are obligatory nose breathers and thus might filter out much of the coarser dust. Conversely, some believe that rodents might overpredict human risk when mechanisms of carcinogenesis that are operative in rodents do not occur in humans (Cohen et al., 1992). It appears that NTP has not seriously explored alternatives to rats and mice in carcinogenesis testing, except perhaps for the use of hamsters in inhalation studies.

In principle, selection of data for estimation of carcinogenic potential from the most sensitive strain or species of animals tested is designed to be conservative; whether it is actually conservative and accurate is unknown. This default assumption contributes to the uncertainty in risk assessment, and research designed to investigate the biological mechanisms of carcinogenesis in both rodents and humans should be vigorously pursued so that more accurate risk assessments can be conducted.

Quantitative Considerations

Key terms in quantitative cancer risk characterization are *unit cancer risk* and *potency*. As currently estimated by EPA, potency is a statistical upper bound on the slope of the linear portion of a dose-response curve at low doses as calculated with a mathematical dose-response model. The unit cancer risk is based on potency and is an upper-bound estimate of the probability of cancer development due to continuous lifetime exposure to one unit of carcinogen. For airborne agents, that unit is commonly defined as exposure to 1 μg of agent per cubic meter of air over a 70-year lifetime.

Cancer potencies are generally based on dose-response relationships generated from cancer bioassays performed with rodents exposed to doses that are several orders of magnitude greater than those for which risk must be estimated. Bioassays typically include two, and to a lesser extent three or more, doses in addition to controls, and are rarely repeated. Often, positive results are obtained at only one dose. Therefore, for most carcinogens, few unequivocal data points are available for potency calculation. In addition, several assumptions often enter into calculations of potency, such as considerations related to tissue dosimetry, in which metabolism data obtained from different experimental systems and used in PBPK modeling might be used in place of bioassay exposure levels. It is not unusual for potency estimates based on the same bioassay data to vary substantially from one risk assessment to another, depending on these additional assumptions and the dose-response model used. Accordingly, potency values

are often fraught with as much uncertainty as other aspects of quantitative risk assessment.

To estimate cancer potencies, EPA currently uses the linearized multistage model (EPA, 1987a). This model uses what is essentially an empirical curvefitting procedure to describe the relationship between bioassay dose and response and to extrapolate the relationship to exposures below the experimental range. A statistical upper bound on the slope of the low-dose linear portion of the curve is considered to represent an upper bound on a chemical's carcinogenic potency. The multistage model is based on a theory of carcinogenic mechanism proposed in the early 1950s by Armitage and Doll. In essence, normal cells in a target organ are envisioned as undergoing a sequence of irreversible genetic transformations culminating in malignancy. Each transformation to a new stage is assumed to occur at some nonzero background rate. Exposure to a carcinogen is presumed simply to increase one or more of the transformation rates in proportion to the magnitude of the exposure (technically, dose at the target site). However, actual exposure circumstances are more complicated than can be briefly described here. No other potential effects of exposure or alternative mechanisms of carcinogenesis, such as induced cell proliferation or receptor-mediated alterations in gene expression, are included in the Armitage-Doll model. One important consequence of this assumption about how exposure influences transformations is the linearity of risk at low doses, i.e., risk increases and decreases in direct proportion to the delivered dose. That result arises in part because the model assumes that the number of cells at risk of undergoing the first transformation (the susceptible target-cell population) is constant and independent of age, magnitude of exposure, and exposure duration. Thus, the normal processes of cell division, differentiation, and death are not taken into account by the model.

Another cancer dose-response model that has been developed to estimate cancer potencies for risk assessment, but that is not used routinely for regulatory purposes, is the two-stage model. The two-stage model was developed by Moolgavkar, Venzon, and Knudson (Moolgavkar and Venzon, 1979; Moolgavkar and Knudson, 1981; Moolgavkar, 1988; Moolgavkar et al., 1988; Moolgavkar and Luebeck, 1990) and postulates that two critical mutations are required to produce a cancer cell. The model presupposes three cell compartments: normal stem cells, intermediate cells that have been altered by one genetic event, and malignant cells that have been altered by two genetic events. The size of each compartment is affected by cell birth, death, and differentiation processes and by the rates of transition between cell compartments. The model can accommodate some current concepts regarding the roles of inactivated tumor-suppressor genes and activated oncogenes in carcinogenesis. Unlike the Armitage-Doll model, it can explicitly account for many processes considered important in carcinogenesis, including cell division, mutation, differentiation, and death and the clonal expansion of populations of cells. Some knowledge of a chemical's mechanism

of action and dose-response data for that mechanism are required to apply the two-stage model, however, and such data on most chemicals are scanty.

Potency estimates are generally based on the assumption that exposure to a particular agent occurs over a 70-year lifetime under constant conditions. That assumption is not likely to apply to the entire exposed population, however, and might produce a conservative estimate of risk. Use of a single potency number implies that the biological response of concern, such as carcinogenesis, depends only on total dose and therefore is independent of dose rate (the quantity of the agent received per unit time). this assumption might be invalid in some cases; for example, studies of low-energy-transfer radiation carcinogenesis show that low-dose-rate exposures are less effective than high-dose-rate exposures (NRC, 1990b). Other studies of radiation have differing results.

Potency estimates provide a means for comparing animal data with human data and for ranking potential carcinogens. Analysis of data available for some 20 known human carcinogens has shown that, in general, potency values derived from carcinogenicity bioassays in animals agree reasonably well with values calculated for humans from epidemiological studies (Allen et al., 1988). However, ranking of chemicals according to potency should not necessarily be used to make conclusions on the ranking of the corresponding hazards or risk. It is only multiplication of potency (unit risk) with exposure (dose) that yields an estimate of risk. Where there is no exposure, there might be little practical need for information on potency.

Evaluation of EPA Practice The selection by EPA of a mathematical model to estimate potency is a critical step in quantitative risk assessment, in which alternative assumptions can lead to large differences in estimated risks. Such a model provides explicit, objective rules for extrapolating from the risks observed in controlled, high-dose laboratory experiments to those associated with the far lower doses that people might receive through inhalation. However, all dose-response models are simplified characterizations of the underlying biological reality. That is due, in part, to the incomplete scientific understanding of toxic mechanisms and to the requirement that the models be usable in a broad array of cases.

The challenge for EPA is to incorporate the expanding knowledge of mechanisms into the design of extrapolation models. The models would then depict more accurately the dose-response relationship at the low doses that are of concern to regulators, but are too low for toxic effects to be directly observed in whole animal studies or, often, any feasible human studies. The challenge can be illustrated by examining the simplified mechanistic assumptions that are included in the multistage model used by EPA in light of new understanding of mechanisms, which is not included in that model.

As long as exposure to a chemical has no substantial effect on cell processes other than genetic change, one would not expect the exclusion of these processes

from the multistage model to compromise the resulting cancer risk estimates. The model would likely be appropriate for "direct-acting" carcinogens—ones, such as radiation, that act by directly attacking cellular DNA and thereby causing genetic transformation. In recent years, however, it has become apparent that many substances alter the pharmacodynamics of cells and can be carcinogenic by mechanisms that do not involve direct covalent interaction with DNA at all, but involve indirectly caused alterations in gene expression. One consequence of such a change could be altered cellular dynamics in the target organ. Because genetic transformations can occur spontaneously, many target organs contain a background of continuing steps in the multistep carcinogenic process. Exposure to a chemical could augment those background carcinogenic processes by simply increasing the pool of cells that are susceptible to further transformation. Such augmentation might occur as a regenerative response to cellular injury among surviving cells or to the cell-killing that occurs after exposure to highly toxic substances. The augmentation of background carcinogenic processes could also occur as an indirect response to alterations in hormonal balances induced by exposure or as a response to a directly mitogenic substance, i.e., one that stimulates normal cell division. By increasing the rate of cell division, such substances can increase the overall probability of generating a mutation, even though they have no direct effect on the transformation probability per cell division.

Similarly, exposure to substances classified as nongenotoxic carcinogens or "promoters" can create physiologic conditions within a target organ that favor the growth of "initiated" cells, i.e., cells that have already sustained at least one irreversible change from normal cells. Clonal expansions of initiated cell populations can be induced by exposure to promoters, thus increasing the probability of cell transformation and malignancy without directly affecting DNA.

Critical to effective regulatory use of biologically based models such as the two-stage model is accurate determination of the dose-response and time-response relationships for agent-induced cell death, differentiation, transformation and division, if any, in target tissues. Those processes might exhibit threshold-like dose-response relationships, in contrast to the presumed low-dose linear response of conventional multistage model transformation rates. Conversely, better understanding might show supralinear relations. Thus, use of a two-stage pharmacodynamic model might predict low-dose risks that are lower or higher than those predicted by the linearized multistage model.

Successful use of biologically based models in the risk assessment process will require a greater variety and amount of information on and understanding of carcinogenic mechanisms than is typically available for most chemicals. In the near term, such a data-intensive approach might be applied only to substances that have great economic value. In the long run, as knowledge and experience accrue, the use of models that incorporate relevant pharmacodynamic data should become more routine. Those models, used in conjunction with pharmacokinetic

models for determining delivered doses, will increase the accuracy of quantitative risk assessment. For that reason, EPA should intensify their incorporation into the cancer-risk assessment process. For more information on two-stage models, see the NRC (1993c) report on this topic.

Carcinogen Classification

As noted in Chapter 4 (Table 4-1), EPA, following the lead of the International Agency for Research on Cancer (IARC), provides an evaluation of the available evidence of carcinogenicity of individual substances. The direction and strength of evidence are summarized by a letter: A, B_1, B_2, C, D, or E (see Table 4-1). The assignment of a substance to a class (actually, the assignment of available evidence to a class) depends almost entirely on epidemiological evidence and evidence derived from animal studies. The evidence for each of these is classified by EPA as "sufficient," "inadequate," or "limited." Some other types of experimental evidence (e.g., on genotoxicity) might sometimes play a role in the classification, but the epidemiological and bioassay data are generally of overriding importance.

The EPA classification scheme is intended to provide information on hazard—not to provide information about potential human risk; the latter cannot be assessed without the additional evaluation of dose-response and exposure information. The assignment of evidence to a class is intended by EPA only to suggest how convinced we should be that a substance poses a carcinogenic hazard to people. The classification is thus meant to depict the state of our knowledge regarding human carcinogenic hazard.

The difference between hazard and risk needs to be further emphasized here. As conceived in EPA's current four-step approach, identifying a substance as a possible, probable, or known carcinogenic hazard to humans means only that, under some unspecified conditions, the substance could cause excess cancers to occur in people. Evaluation of potency and of the exposures incurred by specific populations provides the information needed to assess the probability (risk) that the substance will cause cancer in the specified population. EPA developed the categorization scheme because it believes that, in addition to the risk estimate, decision-makers should have some sense of the strength of the evidence supporting identification of a substance as a carcinogen. There has been some confusion regarding the terms *strength of evidence*, as used by EPA, and *weight of evidence.* Some interpret *strength* to only describe the degree of positive evidence and *weight* to apply when *all* evidence—positive, negative, and evidence on relevance to humans—is considered. The committee adopts those uses of the terms. In many cases, substances for which the evidence of human carcinogenicity is strong (classification A) will, in specific circumstances, pose relatively small risks (because of low potency or low exposure), whereas substances for which the evidence of human carcinogenicity is much less

convincing (classification B_2, for example) are likely to pose large risks (because of high potency or exposure). The typical question faced by a decision-maker is whether, for example, more restrictive controls should be placed on substances in class A that pose relatively small risks or on substances in lower classes that pose equal or greater risks. Stated in other terms, the issue concerns the justification for placing different degrees of regulatory restriction on substances that pose equal risks but which are differently classified. Should we control more carefully substances for which the state of our knowledge regarding human carcinogenicity is highly certain than we do substances for which the state of our knowledge is relatively weak? Although EPA includes a strength-of-evidence classification with each risk characterization, there is no clear indication of whether and how the classification influences ultimate agency decision-making.

Evaluation of EPA Practice Does EPA's approach accurately portray the state of knowledge regarding human carcinogenic hazard? It is certainly the case that the state of scientific knowledge regarding the potential for various substances to contribute to the development of human cancers is highly variable among them. It also seems reasonable that risk assessors should have available a means to express that knowledge in a relatively simple way. It is for this reason that any such scheme should be examined carefully to ensure that it expresses as closely as possible what it is intended to express and that it summarizes all the relevant and appropriate findings derived from data, with no extraneous data.

Because two conclusions (that the substance might pose a carcinogenic hazard to humans under some conditions of exposure and that animal data can be unconditionally extrapolated to humans) are implicitly contained in the current EPA classification system, it could be conceived as misleading in some cases in which the scientific evidence does not support one or more of the typical default assumptions (for example, on route-to-route, high to low dose, or animal-to-human extrapolation). Such a situation could arise when, for example, data are available to show clearly and convincingly that some types of animal tumors would not likely to be produced in humans or when mechanistic data show that results obtained at high doses are not relevant to low doses. Although different in kind, classification of substances at EPA's D or E level could also be misleading. If, for example, a substance were classified at level E on the basis of negative chemical bioassays in two species, but additional data suggested that neither animal species metabolized the substance in the way humans did, then the absence of potential human hazard would be improperly inferred.

The present EPA system might also be misleading because it is too susceptible to "accidents of fate." The carcinogenicity of a substance that happens to cause very rare tumors in humans (e.g., vinyl chloride, which causes angiosarcoma of the liver) is much easier to detect in epidemiological studies than is the carcinogenicity of a substance that causes very common human cancers, such as colorectal carcinoma. Although the available animal data on the latter substance

might be very convincing with respect to carcinogenicity and there might be every reason to believe that it will be as hazardous to humans as the former (i.e., the "known" human, category A carcinogen), it will usually end up in category B, which may be interpreted as suggesting a lesser likelihood of hazard. Such a distinction might be due only to differences in our ability to detect the carcinogenic properties of substances that produce different types of cancers, and not to any true differences in human hazard.

Possible Improvements in EPA Practice Before turning to the issue of improvements in EPA's carcinogen classification scheme, the committee first considered whether any such scheme should be used at all. As noted above, the current scheme can easily be misinterpreted—unfamiliar users might be led to believe that all substances in a specific category are equally hazardous or non-hazardous. Moreover, it is impossible to capture in any simple categorization scheme the completeness and complexity of the information that supports scientific judgments about the nature of a human carcinogenic hazard and the conditions under which it can exist. The quality, nature, and extent of such information vary greatly among carcinogens, and it is not an exaggeration to state that every substance is unique with respect to the scientific evidence bearing on its hazards.

It is for these reasons that the committee strongly recommends that EPA include in each hazard-identification portion of a risk assessment a *narrative* evaluation of the evidence of carcinogenicity. Such a narrative should contain at least the following:

- An evaluation of the strength of the available human and animal evidence.
- A weight-of-evidence evaluation of any available information on the relevance to humans of the animal models used and the results obtained from them and on the conditions of exposure (route, dose, duration, and timing) under which carcinogenic responses to other conditions of exposure (usually conditions that could exist in human populations exposed environmentally) have been measured (either in human populations or in laboratory animals).

Such a narrative seems to be the best way to describe the type of information typically available to evaluate carcinogenic hazards and should be used by EPA when it undertakes full-scale risk assessments.

Although the committee agreed that such narrative descriptions are the preferred way to express scientific evidence, it also recognized that there are important practical needs for some type of simple categorization of evidence. The committee recognized, for example, that many regulatory actions or plans for action require, for practical reasons, the creation of lists of carcinogens and that narrative statements are not likely to be included in such lists. Without some simple categorization scheme, such lists are likely to be completely undiscriminating

with respect to the potential human hazards of the substances on them. When any such lists are used, for example, to create priorities for full risk assessment or for some type of regulation, the results could be seriously misleading to decision-makers and the public.

As already noted, however, the committee believes that the current EPA categorization scheme is inadequate. Substantial improvements could be made if the scheme incorporated not only "strength-of-evidence" information, but also some of the information we have called for in the narrative description.

It will not be easy to create a categorization scheme for carcinogens that incorporates both strength of evidence and the two "relevance" considerations. Moreover, EPA is not the only agency for which such a categorization scheme is useful. Indeed, there is a strong need for international agreement on a single classification. It would be highly desirable for EPA to convene a workshop on the matter and involve other agencies of federal and state governments, IARC, and other national and international bodies to develop a scheme that would have worldwide acceptance. IARC has recently moved to include information on mechanisms of carcinogenic action in its evaluation of carcinogens. Such an effort seems essential to eliminating the deficiencies of current schemes and the confusion that exists because of differences in approaches to categorization around the globe.

The committee suggests the scheme in Table 7-1 as a draft or prototype to avoid the difficulties of the current EPA scheme. The proposal in this table incorporates both strength-of-evidence considerations (as in the current EPA and IARC schemes) and "relevance" information, as specified in the two points mentioned above. The example also reduces the susceptibility of current classification schemes to the "accidents of fate" that can artificially influence the availability of evidence for different substances.

The classification in Table 7-1 takes place in two steps. In Step 1, a classification is made (into Categories I-IV) according to the two relevance criteria mentioned above. Note also that Category I is used for all substances on which positive carcinogenicity data are available and on which there are no substantive data to support conclusions that would place them in Category II or III—i.e., *Category I is the default option that applies when data related to relevance are weak or absent.* Step 2 of the classification involves evaluation of the strength of the available evidence.

Such a categorization scheme can provide guidance on priorities for both risk assessment and a variety of regulatory efforts. Substances placed in Category I, for example, would generally receive greater attention with respect to their carcinogenic properties than those in Category II; and within Category I, the nature of the attention received might be further influenced by the strength of available evidence (i.e., Ia >; b >; c >; d). A Ia substance, for example, might be a prime candidate for immediate and stringent regulation, whereas a Id substance might be a prime candidate for high-priority information-gathering.

TABLE 7-1 Possible Scheme for Categorizing Carcinogens

Step 1: Categorization according to relevance of findings to humans	
Category	Nature of Evidence
Category I Might pose a carcinogenic hazard to humans under any conditions of exposure. Magnitude of risk depends on dose-response relationship and extent of human exposure.	• Evidence of carcinogenicity in either human or animal studies (strength of evidence varies; see Step 2) • No information available to raise doubts about the relevance to humans of animal model or results • No information available to raise doubts about relevance of conditions of exposure (route, dose, timing, duration, etc.) under which carcinogenic effects were observed to conditions of exposure likely to be experienced by human populations exposed environmentally.
Category II Might pose a carcinogenic hazard to humans, but only under limited conditions. Whether a risk exists in specific circumstances depends on whether those conditions exist. Dose-response and exposure assessments must be completed to identify conditions under which risk exists.	• Evidence of carcinogenicity in either human or animal studies (strength of evidence varies; see Step 2) • Scientific information available to show that there are *limitations* in the conditions under which carcinogenicity might be expressed, owing to questions about the relevance to humans of the animal models or results or relevance of the conditions of exposure (route, dose, timing, duration, etc.) under which carcinogenic effects were observed to conditions of exposure likely to be experienced by human populations exposed environmentally.
Category III Notwithstanding the evidence of carcinogenicity in animals, not likely to pose a carcinogenic hazard to humans under any conditions.	• Evidence of carcinogenicity in animal studies • Scientific information available to show that the animal models or results are not relevant to humans under any conditions.
Category IV Evidence available to demonstrate lack of carcinogenicity or no evidence available.	• No evidence of carcinogenicity or evidence of non-carcinogenicity (weight of negative evidence varies; see Step 2)

Step 2: Categorization according to strength of evidence (a through d, in decreasing order of strength)

		Subcategory			
Category	Data Source	a	b	c	d
I	Epidemiology	S	L	NI	NI
	Animal Studies	S/L/NI	S	S	L
II	Epidemiology	s	l	NI	NI
	Animal Studies	s/l/NI	s	s	l
III	Epidemiology	L/NI	NI		
	Animal Studies	s_i	l_i		
IV	Epidemiology	NI	NI/NA		
	Animal Studies	NI	NA		

S = sufficient evidence, high relevance.
L = limited evidence, high relevance.
NI = no or inadequate evidence.
NA = no evidence in adequate studies.
s = sufficient evidence, limited relevance.
l = limited evidence, limited relevance.
s_i = sufficient evidence, low relevance.
l_i = limited evidence, no relevance.

Placement of a substance in Category II does not mean that regulatory efforts should not be undertaken. For example, there might be reason to determine whether potentially risky conditions of exposure exist in any situations. The categories do not influence ultimate actions, but only priorities and the relative, inherent degrees of concern associated with different substances.

Although the committee recommends that any categorization scheme adopted by EPA include the elements associated with the above example, it also recognizes that there might be other ways to capture and express the same information. Some members suggested, for example, that substances listed as carcinogens simply be accompanied by a set of codes that specify both the strength of supporting evidence and the conditions and limitations, if any, that might pertain to the interpretation of that evidence (e.g., an asterisk next to a chemical might mean "assumed to be carcinogenic in humans only when inhaled").

Other End Points of Toxicity

The standard approach to regulating chemicals that are associated with non-cancer end points of toxicity has been based on the theory of homeostasis. According to that theory, biological processes that maintain homeostasis exist in an interdependent web of adaptive responses that automatically react to and compensate

for stimuli that alter optimal conditions. An optimal condition is maintained as long as none of the stimuli that regulate it is pushed beyond some limit or "threshold." For the purposes of regulation, end points of toxicity other than cancer are lumped together under a toxicological paradigm that presumes a dose threshold for any chemical capable of inducing an adverse effect: there is an exposure below which the adverse effect would not be expected to occur. The current approach—no-observed-adverse-effect level (NOAEL) and uncertainty factor—is only a semiquantitative method designed to prevent exposures that are likely to result in an adverse effect, not a mechanistically based quantitative method for assessing the likely incidence and severity of effects in an exposed population. Moving beyond the current simplistic regulatory method will require, as is the case for carcinogenesis, a greater understanding of the mechanisms of disease causation, of pharmacokinetics, and of interindividual variation in each. Such improved understanding will permit final abandonment of the obsolete "threshold versus nonthreshold" paradigm for regulating carcinogens and noncarcinogens.

Evaluation of EPA Practice The methodology now used by EPA to regulate human exposure to noncarcinogens is in a state of flux. That used by EPA in the past was not sufficiently rigorous. It was not based on evaluations of biological mechanisms of action or on differences in susceptibility between and within exposed populations. In addition, it incorporated risk management, not scientifically based risk-assessment techniques; and it did not permit incorporation of newer and better scientific information as it was obtained. The NOAEL-uncertainty factor approach might be adequate for the immediate future as a screening technique and for setting priorities, but its empirical and scientific basis is meager. EPA appears to be continuing to pursue simplistic, empirical techniques by adding to the list of uncertainty factors in use.

Impact of Pharmacokinetic Information in Risk Assessment

One of the critical steps in risk assessment is the selection of the measure of exposure to be used in defining the dose-response relationship. It is common today to calculate exposure on the basis of the "administered dose" of a chemical —the dose or amount fed to animals in toxicity studies or ingested by humans in food or water or inhaled in air. That dose can usually be accurately measured.

The dose that is of interest for risk assessment, however, is the amount of the biologically active form of a substance that reaches specific target tissues. This target-tissue dose is the "delivered dose," and its biologically active derivative, if any, is the "biologically active dose." The biologically active dose causes the events that culminate in toxicity to target cells and organs, and ideally it is used as the basis for defining the dose-response relationship and for assessing risk. The science of pharmacokinetics seeks to replace the current operating

assumption—that administered dose and delivered dose are always directly proportional and that the administered dose is therefore an appropriate basis for risk assessment—with direct, accurate information about the delivered or biologically active dose.

Pharmacokinetic models are used to study the quantitative relationship between administered and delivered or biologically active doses. The relationship reflects the spectrum of biological responses to exposure, from physiological responses of a whole organism to biochemical responses within specific cells of a target organ. Pharmacokinetic models explicitly characterize biologic processes and permit accurate predictions of the doses of an agent's active metabolites that reach target tissues in exposed humans. As a consequence, the use of pharmacokinetic models to provide inputs to dose-response models reduces the uncertainty associated with the dose parameter and can result in more accurate estimates of potential cancer risks in humans.

The relationship between administered and delivered doses often differs among individuals: because of such differences, some people might be acutely sensitive and others insensitive to the same administered dose. The relationship between administered and delivered doses can also differ between large and small exposures and between continuous and intermittent exposures, and it can differ among species, some species being more or less efficient than humans in the transport of an administered dose to tissues or in its metabolism to a biologically active or inactive derivative. Those differences in the relationship between administered and delivered or biologically active doses can dramatically affect the validity of the predictions of dose-response models; failure to incorporate the difference into the models contributes to the uncertainty in risk assessment.

Differences between administered and biologically active doses occur because specialized organ systems intervene to modulate the body's responses to inhaled, ingested, or otherwise absorbed toxic materials. For example, the liver can detoxify materials circulating in the blood by producing enzymes to accelerate chemical reactions that break the materials down into harmless components (metabolic deactivation, or "detoxification"). Conversely, some substances can be activated by metabolism into more toxic reaction products. Activation and detoxification might occur at the same time and can occur in the same or different organ systems.

Furthermore, the rates at which activation and detoxification take place might have natural limits. Metabolic deactivation might thus be overwhelmed by high exposure concentrations, as seems to be the case with formaldehyde: the biologically active dose and the risk of nasal-tumor development rise rapidly in exposed rats only at high airborne concentrations. The assumption of a simple linear relationship between administered and biologically active doses of formaldehyde is believed by many to result in exaggerated estimates of cancer risk at low exposure concentrations. In contrast, metabolic activation of vinyl chloride occurs more and more slowly with increasing administered dose, because a critical

enzyme system becomes overloaded; the biologically active dose and the resulting liver-tumor response increase more and more slowly as the administered dose increases. The assumption of a linear relationship between administered and delivered doses in the case of vinyl chloride could result in underestimation of the cancer risk associated with low doses. These examples illustrate how using pharmacokinetic models can reduce the uncertainty in risk estimation by modifying the dose values used in dose-response modeling to reflect the nonlinearity of metabolism.

Although most pharmacokinetic models are derived from laboratory-animal data, they provide a biological framework that is useful for extrapolating to human pharmacokinetic behavior. Anatomical and physiological differences among species are well documented and easily scaled by altering model parameters for the species in question. This aspect of pharmacokinetic modeling reduces the uncertainty associated with extrapolating from animal experiments to human cancer risk. For example, considerable effort has been devoted to the development of pharmacokinetic models for methylene chloride, which is considered a rodent carcinogen. The model was initially developed on the basis of rat data, then scaled to predict human behavior. Predictions in humans were compared with published data and with the results of experiments in human volunteers. The model was shown to predict accurately the pharmacokinetic behavior of inhaled methylene chloride and its metabolite carbon monoxide in both species (Andersen et al., 1991). Use of a particular pharmacokinetic model for methylene chloride in cancer risk assessment reduces human risk estimates for exposure to methylene chloride in drinking water by a factor of 50-210, compared with estimates derived by conventional linear extrapolation and body surface-area conversions (Andersen et al., 1987). Other analyses show different results (Portier and Kaplan, 1989). What pharmacokinetic models for methylene chloride do not predict, however, is whether methylene chloride is a human carcinogen. Thus, although use of the model might improve confidence in dose estimation by replacing the conventional scaling-factor approach, it cannot predict the outcome of exposure in humans.

Another way to reduce uncertainty would be to use pharmacokinetic models to extrapolate between exposure routes. If information on the disposition of an agent were available only as a result of its inhalation in the workplace, for example, and a risk assessment were required for its consumption in drinking water, appropriate models could be constructed to relate the delivered dose after inhalation to that expected after ingestion. To the committee's knowledge, pharmacokinetic models have not yet been used in a risk assessment for such regulatory purposes.

Failure to include pharmacokinetic considerations in dose-response modeling contributes to the overall uncertainty in a risk assessment, but uncertainty is associated with their use as well. This uncertainty comes from several sources. First, uncertainty is associated with the pharmacokinetic model parameters themselves.

Parameter values are usually estimated from animal data and can come from a variety of experimental sources and conditions. Quantities can be measured indirectly, they can be measured *in vitro*, and they can vary among individuals. Different data sets might be available to estimate values of the same parameters. Hattis et al. (1990) evaluated seven pharmacokinetic models for tetrachloroethylene (perchloroethylene) metabolism and found that their predictions varied considerably, primarily because of the differences in choice of data sets used to estimate values of model parameters. Moreover, analogous parameter values are also needed for humans—although some values, such as organ weights, are amenable to direct measurement and do not vary widely among humans, others, such as rate constants for enzymatic detoxification and activation, are both difficult to measure and highly variable.

Second, there is uncertainty in the selection of the appropriate tissue dose available to model. For example, information might be available on the blood concentration of an agent, on its concentration in a tissue, or on the concentrations of its metabolites in the tissue. Tissue concentrations of one metabolite might be inappropriate if another metabolite is responsible for the biologic effects. Total tissue concentrations might not accurately reflect the biologically active dose if only one type of cell within the tissue is affected.

Choice of an appropriate measure of tissue dose can have an effect on cancer risk estimates. Farrar et al. (1989) considered three measures of tissue dose for tetrachloroethylene: tetrachloroethylene in liver, tetrachloroethylene metabolites in liver, and tetrachloroethylene in arterial blood. Using EPA's pharmacokinetic model for tetrachloroethylene and cancer bioassay data in mice, they found that human cancer risk estimates varied by a factor of about 10,000, depending on the dose surrogate used. Interestingly, the estimates bracketed that obtained in the absence of any pharmacokinetic transformation of dose as shown in Table 7-2.

This example illustrates the variation in dose and risk estimates that can be obtained under different assumptions, but it does not help to evaluate of the

TABLE 7-2 Risk Estimates Based on EPA's Pharmocokinetic Model for Tetrachloroethylene and Cancer Bioassay Data in Mice

Dose Surrogate	Risk Estimate[a]
Administered dose	5.57×10^{-3}
Dose to liver	425×10^{-3}
Dose of metabolites to liver	0.0195×10^{-3}
Dose in blood	126×10^{-3}

[a] Maximum-likelihood estimate.

SOURCE: Adapted from Farrar et al., 1989.

validity of any of the estimates in the absence of knowledge of the biologic mechanism of action of tetrachloroethylene as a rodent carcinogen and in the absence of knowledge of whether it is a human carcinogen. Although the dose of metabolites to the liver appears to be the most appropriate choice of dose surrogate, there is a high degree of nonlinearity between this dose and the tumor incidence in mice. The nonlinearity indicates either that this dose surrogate does not represent the actual biologically active dose for the particular sex-species combination analyzed by these authors or that the model does not adequately describe tetrachloroethylene pharmacokinetics.

The science of pharmacokinetics seeks to gain a clear understanding of all the biological processes that affect the disposition of a substance once it enters the body. It includes the study of many active biological processes, such as absorption, distribution, metabolism (whether activation or deactivation), and excretion. Accurate prediction of delivered and biologically active doses requires comprehensive, physiologically based computer models of those linked processes. Because the science of pharmacokinetics aims to replace general assumptions with a more refined model based on the specific relationship between administered and delivered or biologically active doses, its use in risk assessment will help to reduce the uncertainties in the process and the related bias in risk estimation. Advances will come slowly and at considerable cost, because detailed knowledge of the biologically active dose of many materials must be acquired before generalizations can be confidently exploited. Nevertheless, EPA increasingly incorporates pharmacokinetic data into the risk-assessment process, and its use represents one of the clearest opportunities for improving the accuracy of risk assessments.

Conclusions

Developing improved methods for assessing the long-term health impacts of chemicals will depend on improved understanding of the underlying science and on more effective coordination, validation, and integration of the relevant environmental, clinical, epidemiological, and laboratory data, each of which is limited by various kinds of error and uncertainty. Goodman and Wilson (1991) have demonstrated that, for 18 of 22 chemicals studied, there is good agreement between risk estimates based on rodent data and on epidemiologic studies. Their quantitative assessment, which can be compared to the Ennever et al. (1987) qualitative evaluation of the same issue, provides stronger evidence that current risk-assessment strategies produce reasonable estimates of human experience for known human carcinogens (Allen et al., 1988).

The reliability of a given health-risk assessment can be determined only by evaluating both the validity of the overall assessment and the validity of its components. Because the validity of a risk assessment depends on how well it predicts health effects in the human population, epidemiologic data are required

for testing the predictions. To the extent that the requisite data are not already available, epidemiologic research will be necessary. An example is the study in which the New York Department of Health conducted biological monitoring for arsenic in schoolchildren (New York Department of Health, 1987). The researchers compared their findings with the arsenic concentrations predicted by the risk assessment conducted by EPA. The good agreement between the estimates and actual urinary arsenic concentrations in the children provided support for the EPA risk model.

The committee believes that substantial research is warranted to validate methods, models, and data that are used in risk assessment. In some instances the magnitude of uncertainty is not well understood, because information on the accuracy of the prediction process for each model used in risk assessment is insufficient. We also note that the uncertainties tend to vary considerably; for example, uncertainties are relatively low for estimation of population characteristics, compared with those associated with extrapolation from rodents to human beings.

The quality of risk analysis will improve as the quality of input improves. As we learn more about biology, chemistry, physics, and demography, we can make progressively better assessments of the risks involved. Risk assessment evolves continually, with re-evaluation as new models and data become available. In many cases, new information confirms previous assessments; in others, it necessitates changes, sometimes large. In either case, public confidence in the process demands that EPA make the best judgments possible. That an estimate of risk is subject to change is not a criticism of the process or of the assessors. Rather, it is a natural consequence of increasing knowledge and understanding. Re-evaluating risk assessments and making changes should be expected, embraced, and applauded, rather than criticized.

Findings And Recommendations

The following is a compilation of findings and recommendations related to evaluation of methods, data, and models for risk assessment.

Predictive Accuracy and Uncertainty of Models

Various methods and models are available to EPA and other organizations for conducting emission characterization, exposure assessment, and toxicity assessments. They include those used as default options and their corresponding alternatives, which represent deviations from the defaults. The predictive accuracy and uncertainty of the methods and models used for risk assessment are not clearly understood or fully disclosed in all cases.

- EPA should establish the predictive accuracy and uncertainty of the methods and models and the quality of data used in risk assessment with the high

priority given to those which support the default options. EPA and other organizations should also conduct research on alternative methods and models that might represent deviations from the default options to the extent that they can provide superior performance and thus more accurate risk assessments in a clear and convincing manner.

Emission Characterization

Guidelines

EPA does not have a set of guidelines for emission characterization to be used in risk assessment.

- EPA should develop guidelines that require a given quality and amount of emission information relative to a given risk-assessment need.

Uncertainty

EPA does not adequately evaluate the uncertainty in the emission estimates used in risk assessments.

- Because of the wide variety of processes and differing maintenance of those sources, EPA should develop guidelines for the estimation and reporting of uncertainty in emission estimates; these guidelines may depend on the level of risk assessment.

External Collaboration

EPA has worked with outside parties to design emission characterization studies that have moved the agency from crude to more refined emission characterization.

- EPA should conduct more collaborative efforts with outside parties to improve the overall risk-assessment process, and each step within that process.

Exposure Assessment

Gaussian-Plume Models

In its regulatory practice, EPA has relied on Gaussian-plume models to estimate the concentrations of hazardous pollutants to which people are exposed. However, Gaussian-plume models are crude representations of airborne transport processes; because they are not always accurate, they lead to either underestimation or overestimation of concentrations. Stochastic Lagrangian and photochemical models exist, and evaluations have shown good agreement with

observations. Also, EPA has typically evaluated its Gaussian-plume models for release and dispersion of criteria pollutants from plants with good dispersion characteristics (i.e., high thermal buoyancy, high exit velocity, and tall stacks). EPA has not fully evaluated the Gaussian-plume models for hazardous air pollutants with realistic plant parameters and locations; thus, their potential for underestimation or overestimation has not been fully disclosed.

- EPA should evaluate the existing Gaussian-plume models under more realistic conditions of small distances to the site boundaries, complex terrain, poor plant dispersion characteristics (i.e., low plume buoyancy, low stack exit momentum, and short stacks), and presence of other structures in the plant vicinity. When there is clear and convincing evidence that the use of Gaussian-plume models leads to underestimation or overestimation of concentrations (e.g., according to monitoring data), EPA should consider incorporating state-of-the-art models, such as stochastic-dispersion models, into its set of concentration-estimation models and include a statement of criteria for their selection and for departure from the default option.

Exposure Models

EPA has not adequately evaluated HEM-II for estimation of exposures, and prior evaluations of exposure models have shown substantial discrepancies between measured and predicted exposures, i.e., yielding under prediction of exposures.

- EPA should undertake a careful evaluation of all its exposure models to demonstrate their predictive accuracy (via pollutant monitoring and assessment of model input and theory) for estimating the distribution of exposures around plants that limit hazardous air pollutants. EPA should particularly ensure that, although exposure estimates are as accurate as possible, the exposure to the surrounding population is not underestimated.

Population Data

EPA has not previously used population activity, population mobility, and demographics in modeling exposure to hazardous air pollutants and has not adequately evaluated the effects of assuming that the population of a census enumeration district is all at the location of the district's population center.

- EPA should use population-activity models in exposure assessments when there is reason to believe that the exposure estimate might be inaccurate (e.g., as indicated by monitoring data) if the default option is applied. This is particularly important in the case of potential underestimation of risk. Population mobility and demographics will also play a role in determining risk and lifetime exposures. EPA should conduct further evaluation of the use of both simple methods

(e.g., use of center of the population examined) and more comprehensive tools (e.g., NEM and SHAPE exposure models).

Human-Exposure Model

EPA uses the Human-Exposure Model (HEM) to evaluate exposure associated with hazardous air-pollutant releases from stationary sources. This model generally uses a standardized EPA Gaussian-plume dispersion model and assumes nonmobile populations residing outdoors at specific locations. The HEM construct will not provide accurate estimates of exposure in specific locations and for specific sources and contaminants where conditions do not match the simplified exposure and dispersion-model assumptions inherent in the standard HEM components.

- EPA should provide a statement on the predictive accuracy and uncertainty associated with the use of the HEM in each exposure assessment. The underlying assumption that the calculated exposure estimate based on the HEM is a conservative one should be reaffirmed; if not, alternative models whose performance has been clearly demonstrated to be superior should be used in exposure assessment. These alternative models should be adapted to include both transport and personal activity and mobility into an exposure-modeling system to provide more accurate, scientifically founded, and robust estimates of pollutant exposure distributions (including variability, uncertainty, and demographic information). Consideration may be given to linking these models to geographic information systems to provide both geographic and demographic information for exposure modeling.

  EPA generally does not include non-inhalation exposures to hazardous air pollutants (e.g., dermal exposure and bioaccumulation); its procedure can lead to underestimation of exposure. Alternative routes can be an important source of exposure. Modeling systems similar to extensions of HEM have been developed to account for the other pathways.
- EPA should explicitly consider the inclusion of noninhalation pathways, except where there is prevailing evidence that noninhalation routes—such as deposition, bioaccumulation, and soil and water uptake—are negligible.

Assessment of Toxicity

Extrapolation from Animal Data for Carcinogens

EPA uses laboratory-animal tumor induction data, as well as human data, for predicting the carcinogenicity of chemicals in humans. It is prudent and reasonable to use animal models to predict potential carcinogenicity; however, additional information would enhance the quantitative extrapolation from animal models to human risks.

- In the absence of human evidence for or against carcinogenicity, EPA should continue to depend on laboratory-animal data for estimating the carcinogenicity of chemicals. However, laboratory-animal tumor data should not be used as the exclusive evidence to classify chemicals as to their human carcinogenicity if the mechanisms operative in laboratory animals are unlikely to be operative in humans; EPA should develop criteria for determining when this is the case for validating this assumption and for gathering additional data when the finding is made that the species tested are irrelevant to humans.

  EPA uses data that generally assume that exposure of rats and mice after weaning and until the age of 24 months is the most sensitive and appropriate test system for conservatively predicting carcinogenicity in humans. These doses miss exposure of animals before they are weaned including newborns. Furthermore, the sacrifice of animals at the age of 2 years makes it difficult to estimate accurately the health affects of a disease whose incidence increases with age (as does that of cancer).
- EPA should continue to use the results of studies in mice and rats to evaluate the possibility of chemical carcinogenicity in humans. EPA and NTP are encouraged to explore the use of alternative species to test the hypothesis that results obtained in mice and rats are relevant to human carcinogenesis, the use of younger animals when unique sensitivity might exist for specific chemicals, and the age-dependent effects of exposure.

  EPA typically extrapolates data from laboratory animals to humans by assuming that the delivered dose is proportional to the administered dose, as a default option. Alternative pharmacokinetic models are used less often to link exposure (applied dose) to effective dose.
- EPA should be encouraged to continue to explore and, when it is scientifically appropriate, incorporate mechanism-based pharmacokinetic models that link exposure and biologically effective dose.

The location of tumor formation in humans is related to route of exposure, chemical properties, and pharmacokinetic and pharmacodynamic factors, including systemic distribution of chemicals throughout the body. Thus, tumors might be found at different sites in humans and laboratory animals exposed to the same chemical. EPA has accepted evidence of carcinogenicity in tissues of laboratory animals as evidence of human carcinogenicity without necessarily assuming correspondence on a tumor-type or tissue-of-origin basis. EPA has extrapolated evidence of tumorigenicity by one route to another route where route-specific characteristics of disposition of the chemical are taken into account. EPA has traditionally treated almost all chemicals that induce cancer in a similar manner, using a linearized multistage nonthreshold model to extrapolate from large exposures and associated measured responses in laboratory animals to small exposures and low estimated rates of cancer in humans.

- Pharmacokinetic and pharmacodynamic data and models should be validated, and quantitative extrapolation from animal bioassays to humans should continue to be evaluated and used in risk assessments. EPA should continue to use the linearized multistage model as the default for extrapolating from high to low doses. If information on the mechanism of cancer induction suggests that the slope of the linearized multistage model is not appropriate for extrapolation, this information should be made an explicit part of the risk assessment. If sufficient information is available for an alternative extrapolation, a quantitative estimate should be made. EPA should develop criteria for determining what constitutes sufficient information to support an alternative extrapolation. The evidence for both estimates should be made available to the risk manager.

Extrapolation of Animal Data on Noncarcinogens

EPA uses a semiquantitative NOAEL-uncertainty factor approach to regulating human exposure to noncarcinogens.

- EPA should develop biologically based quantitative methods for assessing the incidence and likelihood of noncancer effects in an exposed population. These methods should permit the incorporation of information on mechanisms of action, as well as on differences in population and individual characteristics that affect susceptibility. The most sensitive end point of toxicity should continue to be used for establishing the reference dose.

Classification of Evidence of Carcinogenicity

EPA's narrative descriptions of the evidence of carcinogenic hazards are appropriate, but a simple classification scheme is also needed for decision-making purposes. The current EPA classification scheme does not capture information regarding the relevance to humans of animal data, any limitations regarding the applicability of observations, or any limitations regarding the range of carcinogenicity outside the range of observation. The current system might thus understate or overstate the degree of hazard for some substances.

- EPA should provide comprehensive narrative statements regarding the hazards posed by carcinogens, to include qualitative descriptions of both: 1) the strength of evidence about the risks of a substance; and 2) the relevance to humans of the animal models and results and of the conditions of exposure (route, dose, timing, duration, etc.) under which carcinogenicity was observed to the conditions under which people are likely to be exposed environmentally. EPA should develop a simple classification scheme that incorporates both these elements. A similar scheme to that set forth in Table 7-1 is recommended. The agency should seek international agreement on a classification system.

Potency Estimates

EPA uses estimates of a chemical's potency, derived from the slope of the dose-response curve, as a single value in the risk-assessment process.

- EPA should continue to use potency estimates—i.e., unit cancer risk—to estimate an upper bound on the probability of developing cancer due to lifetime exposure to one unit of a carcinogen. However, uncertainty about the potency estimate should be described as recommended in Chapter 9.

Although EPA routinely cites available human evidence, it does not always rigorously compare the quantitative risk-assessment model based on rodent data with available information on molecular mechanisms of carcinogenesis or with available human evidence from epidemiological studies.

- Because the validity of the overall risk-assessment model depends on how well it predicts health effects in the human population, EPA should acquire additional expertise in areas germane to molecular and mechanistic toxicology. In addition, EPA should also acquire additional epidemiological data to assess the validity of its estimates of risk. These data might be acquired in part by formalizing a relationship with the National Institute for Occupational Safety and Health to facilitate access to data from occupational exposures.

8

Data Needs

This chapter discusses the quantity, quality, and availability of data needed for conducting an adequate risk assessment in the context of the Clean Air Act Amendments of 1990 (CAAA-90). It begins by discussing the need for a priority-setting process, and the need for an iterative data-collection process. It then indicates the proper prioritization for data collection and the availability of data in each of the key risk-assessment steps. It concludes with a discussion of how data should be managed.

Context Of Data Needs

Most would agree that, given the best available model, additional relevant data will lead to a more accurate and precise risk assessment. The quality of the data is critical, no matter how excellent the model chosen, to avoid the classic "garbage in, garbage out" problem. In the gathering of data, tradeoffs must often be made among data that are necessary, data that are desirable, and data that are affordable. Desirability must be defined in the context of the risk-management goals to be achieved, which might be the development of regulations, the setting of standards, or the screening of chemicals to set priorities.

The more precisely the risk manager frames the questions to be addressed by the risk assessment at the outset, the less ambiguity there will be as to what data are required to answer the questions, the less need for judgment in datagathering, and the lower the likelihood that inappropriate or insufficient data will be gathered. As a corollary, public input into the framing of goals and questions can help to avoid public criticism and distrust of the process of risk assessment,

including the gathering of exposure and toxicity data. Public confidence that risk managers are addressing real concerns, as opposed to going through a process perfunctorily, is critical to the future of risk assessment as an activity capable of improving the quality of life. Risk managers need to articulate clearly from the beginning who is to be protected from what, when and where, and at what cost (including how much effort and funds are to be expended to collect appropriate data), so that risk assessors can provide relevant information.

Implications For Priority-Setting

It is not necessary, nor would it be cost-effective, to collect all the data needed for a complete health-hazard assessment on all the 189 chemicals (or mixtures) listed in CAAA-90. It is important, however, that the entire list be examined to identify chemicals that are potentially hazardous and that the later full-scale evaluation of each chemical selected for further scrutiny proceed as effectively as possible. An overall strategy is essential for setting priorities among the steps in the information-gathering process and for determining the extent of assessment needed.

Because risk is a function of exposure, as well as toxicity, determining both that a chemical is of low toxicity to all humans and that all humans have only small exposures to it would lead to an overall low priority for a full-scale risk assessment. Obviously, assigning a high priority to both would lead to an overall high priority for such assessment and argue for collection of a complete data set in all categories of exposure and toxicity. There will be various intermediate levels between low and high overall priority.

In the absence of pertinent human data, toxicological evaluation should begin with the simplest, most rapid, and most economical tests and proceed to more complex, time-consuming, and more expensive tests only as warranted by the initial steps. Similarly, emission, transport, and exposure data might be used to rank chemicals for testing, from those with relatively large exposure potential down to those with a very low likelihood of significant exposure, either for the population at large or for any substantial subset of the population. What is "substantial" in this context will of course depend on concurrent assessments of toxicity. Ordering can then be based on an evaluation of a relatively modest or limited data set.

To assess whether there is a potential for exposure, and to gauge the magnitude and duration of exposure, one needs to know:

1. Is the chemical emitted into the air?
2. Is the chemical stable enough to be transported from its source to a population?

If the chemical is not emitted or is so unstable that it breaks down into innocuous products before reaching a population, no further data need be collected

and further risk assessment is not warranted. But if it is emitted and can be transported to a population, one needs to ask:

3. Who is exposed, to how much, and for how long?
4. What is the relationship between exposure (dose) and response (effect) for humans and for animals?

In an iterative data-collection process, one works through data related to questions 1-4, first collecting the most critical data within each category, then judging needs for more data within that category before moving to the next category. The process is iterative until sufficient information is gathered to draw a conclusion—e.g., on a potential threat to public health.

Section 112 of the Clean Air Act mandates that EPA consider the hazards and possible regulation of 189 specified chemicals. Considering both the effort required to carry out complete risk assessments and the resources of the agency, it is unlikely that that can be accomplished within the time constraints of the act. Consequently, in the spirit of the act and in the interest of the public welfare, it is critical that EPA assign priorities to the chemicals listed. These priorities should be based first on their potential impact on human health and welfare.

Some of the 189 chemicals appear to present major problems because of their variety of sources, large exposures, or high potency. Other chemicals present simpler problems—e.g., some have relatively few sources, some have lower potential for human exposures, and some have very low potency. It is an inefficient use of resources to invest huge amounts of money and time in research and analysis to determine factors already known to be inconsequential for final risk assessment or to confirm credible estimates on which consensus can easily be obtained. Therefore, EPA should do preliminary analyses (screenings) on all listed compounds to ascertain which chemicals merit detailed risk-assessment efforts and which do not merit such work. These preliminary analyses should be reviewed by an independent board to ensure the validity of the resulting priorities for full-scale assessments. Priorities should be continually reevaluated and changed as appropriate in response to new data. The task of setting priorities and keeping them up to date is not trivial and should be specifically included, with adequate resources, in EPA's evolving program plan to implement CAAA-90. The iterative data-collection process can then help in setting priorities for ranking needed studies to avoid the accumulation of a surfeit of data, which would result in misuse of funds and waste of time.

Data Needed For Risk Assessment

The following sections discuss the priority-setting and availability of data for each of the key data-processing steps in risk assessment: emissions, environmental fate and transport, exposure, and toxicity. The final section summarizes the data priorities in each of these areas, and indicates how this data can be used for overall priority-setting for data collection.

Emissions

Knowledge of emissions of a chemical into the air—specifically, the quantity emitted per unit of time (flux) from each place where it is made, stored, used, or disposed of plus its physical and chemical form—is fundamental to characterizing the magnitude of expected exposure to the chemical.

Priorities for Collecting Data

The specific methods for characterizing emissions are described and evaluated in Chapter 7. On the basis of this analysis, an iterative data-collecting process for emission characterization might proceed roughly as follows:

1. Plant-specific material balance
2. Industry-wide emission factors
3. Plant-specific emission factors
4. Facility measurements, including flux determinations.

Data quality is critical, because of the wide variety of emission-estimation techniques and the many types of facilities emitting hazardous air pollutants. EPA often uses whatever data are available at the time of decision-making and has not published guidelines or standards for the quality of emission data to be used in its risk assessments.

Because the emission-characterization database is extremely important for priority-setting, EPA should review the emission estimates submitted to ensure that they meet reasonable quality standards and that emission estimates from all sources within a site are submitted.

Data Availability

EPA plans to use emission information that is available in the Toxic Release Inventory (TRI) database as required by Title III of the Superfund Amendments and Recovery Act (SARA). The information available in this database is shown in the table provided by EPA to the committee in Appendix A. The TRI database includes information on annual emissions, facility location, and categorization of emissions as fugitive, point source, or both.

These data have two serious limitations for any use in risk assessment. First, the database does not include emissions from all operations at a facility; for example, transfer operations are not reported. Second, the database does not include emissions of less than 10 tons/year, nor does it have the locations of emission points or the frequency of emissions. Some information is available in emission inventory databases that are required by state implementation plans (SIPs) that states are required to submit to EPA to indicate how they plan to control emissions relative to CAAA-90, but that information is not necessarily

well characterized. For example, emissions of volatile organic chemicals (VOCs) might be listed as a total, instead of as emissions of separate chemicals; but risk assessments should generally be done for separate chemicals, rather than for classes of chemicals.

A study by Amoco and EPA (1992) gives an example of the differences between estimated or calculated emissions (such as those listed in the TRI database) and emissions determined via direct measurement. This study found that the "existing estimates of environmental releases were not adequate for making a chemical-specific, multi-media, facility wide assessment." The report identified several specific problems in using the TRI database to conduct an in-depth evaluation of a facility:

- Lack of chemical characterization data.
- Difficulty of measuring and characterizing small sources.
- Use of estimated, rather than actual, data.
- Lack of identification of new sources leading to underestimation.
- Overestimation of some sources because of use of standardized industry-wide emission factors.
- No requirement that all chemicals be reported in the TRI database (e.g., only 9% of total hydrocarbons were required to be reported).
- Exclusion of some activities and emissions from record-keeping requirements (e.g., barge loading, which accounted for about 20% of benzene emissions).
- Lack of data in TRI on location of nearby populations and ecosystems.

EPA should develop a mechanism to gather the information just listed in a consistent fashion. This mechanism could include changes in Title III of SARA, which requires the TRI reporting requirement or development of information for Title I or V of CAAA-90. Although development of emission characterization databases for all of the 189 chemicals might initially seem to be a major task, CAAA-90 requires states to develop more detailed emission inventories by November 1992 and to update them. Most facilities are then required to estimate their emissions on a point basis to satisfy state requirements for emission inventories. Much of this information is also required for permit purposes.

Even simple changes, such as modifying the SARA Title III requirements to include all 189 hazardous air pollutants on the list, would help. Sixteen of the 189 compounds in CAAA-90 Title III are not on the TRI list (see Table 8-1). In addition, the TRI database includes only sources that have 10 or more full-time employees and that manufacture, process, or use specified chemicals above a certain production rate. That restriction excludes smaller sources within the manufacturing sector for which risk assessments must be conducted under the Title III requirements. Instituting an emission threshold relative to the Title III requirements (e.g., 10 tpy for single compound; 25 tpy for multiple compounds) might be more appropriate for gathering information for risk-assessment purposes.

TABLE 8-1 List of Section 112 Pollutants Not in Toxic Release Inventory Data Base

2,2,4-Trimethyl pentane
Acetophenone
Caprolactan
Dichlorodiphenyldichloroethylene (DDE)
Dimethyl formanide
Fine mineral fibers
1 texamethylene-t,t,-diisocyanate
Hexane
Isophorone
Phosphine
Polycylic organic matter
Sulfur dioxide, anhydrous
TCDD
Triethylamine

For evaluation of VOCs, many of which are on the list of 189 compounds under Title III, emission estimates developed for other regulatory purposes (such as the ozone provisions of CAAA-90) can be used. However, these data are frequently not speciated in terms of the chemical composition of the VOCs. In addition, the reporting of VOC emission information is required only in nonattainment areas, so this information may not always be available.

Environmental Fate and Transport

Emitted pollutants can move within and between environmental media and be converted to different forms. A thorough understanding of what happens to a chemical in the environment forms part of the basis for estimating human exposure and hence determining risk.

Priorities for Collecting Data

In the proposed iterative data-collection process described at the beginning of this chapter, data on environmental fate and transport would be acquired in roughly the following order:

1. Physical properties.
2. Physicochemical properties of environment.
3. Chemical properties or reactivity.
4. Rates of potential removal processes.

Once that information is available, a model calculation of expected concentrations

in nearby air is relatively straightforward. If the information is not available, it must be obtained or assumed.

Data Availability

Data on emissions and physical properties are generally available or can be estimated (Lyman et al., 1982). For chemical properties and reactivity, they are available for some environmental reactions, but not all. In the case of physicochemical properties, the environment data are generally available at most locations in the United States. Information on the rates of potential removal processes are more difficult and costly to obtain.

Careful evaluation of data is necessary. For example, published vapor pressures of organic chemicals of moderate to low volatility determined under laboratory conditions can be seriously inaccurate and misleading. For all chemicals, vapor-phase reaction rate constants, when extrapolated from the laboratory to outdoor ambient air, can be seriously in error. The literature is not always for purposes of risk assessment.

Exposure

Accurate exposure data are crucial to valid risk assessment. For example, exposure data must match up temporally with the health end points of concern. Key issues in the evaluation of exposure are

- The end points of interest (e.g., acute vs. chronic toxicity).
- The populations at risk (i.e., the general population and defined subpopulations with potentially increased risks).
- The routes of exposure (e.g., air, diet, or skin).
- The duration (e.g., lifetime, annual, or instantaneous).
- The nature and degree of simultaneous toxicant exposures.

Rarely are all those issues resolved by the exposure data available for a risk assessment. Efforts to collect the data should focus on the minimum needed to meet the goals of the assessment in its risk-management context.

Priorities for Collecting Data

In the proposed iterative data-collection process, the order of data collection might be as follows:

1. *Ambient-air monitoring.* Most commonly, ambient-air monitoring produces interval concentrations in samples averaged over a fixed time, such as 8 hr or 24 hr at fixed sampling stations. The number of stations, their times of operation, and their locations relative to known emission sources and populations

at risk must be known, as well as concentration averages, variances or ranges (to estimate uncertainty), and a description of the methods used, including potential error. The time interval of ambient-air monitoring should be commensurate with the time needed to elicit the physiological effects of concern.

2. *Targeted fixed-point monitoring data*. These data are often generated from samples placed near sources of high-volume emissions (i.e., "hot spots") or in response to some real or perceived public-health need. They should be accompanied by the same information as for ambient-air monitoring. Targeted monitoring is often more useful than monitoring at pre-existing sampling stations if it can focus on higher concentrations of a pollutant, a population at greater risk, or both.
3. *Peak-concentration data*. Either ambient-air or targeted monitoring can miss peak concentrations, because the sampling interval is so long as to "average out" all peaks and valleys in the sampled air mass. Sampling with instantaneous analyzers (e.g., spectrophotometers) or interval analyzers that can accept a sample of short duration is needed to define peaks. That might be of special importance for a toxicant released intermittently.
4. *Personal monitoring*. Concentration data from personal monitors are often more useful for risk assessment, because they show the exposure of individual subjects and can be used to relate activity patterns to exposure. If enough subjects are selected for monitoring, a population exposure can be constructed. Such information is not yet generally available, except for a few toxicants, because of the time and expense of a comprehensive study. This in turn is primarily due to a lack of low-cost, portable sampling devices for most chemicals. Active samplers may provide more information directly for risk assessment than passive samplers for personal monitoring, because pollutant concentrations (and thus the dose) can be estimated more directly with active sampling. Passive samplers do not provide specific concentrations; however, they are far less costly and bulky than active samplers. They are useful in screening (i.e., to determine whether exposure has occurred). Research to correlate the concentrations detected by passive samplers with exposure and dose would further enhance their potential.
5. *Biological markers*. If a toxicant produces a metabolite, enzyme alteration, or other signal that exposure has occurred and so leads to a high correlation between that marker and degree of exposure, such information can reduce the uncertainty in a predicted risk and could be useful for risk assessment. In one respect, this would be the best exposure information, because it would show that the toxicant has been absorbed and has already had some biological effect (NRC, 1987); but it makes single-source exposure assessment difficult, because it reveals total uptake across all routes of exposure. Unless biologic-marker data are checked against external exposure data, they cannot be used to determine dose. Validation of the correlation between an external concentration and the magnitude of a biological marker in experimental animals can be helpful, but

one is left with the difficulty of extrapolating to humans, who may not respond in the same quantitative way as experimental animals. In some cases, markers in humans can be established in occupational settings.

Data Availability

Some of the 189 chemicals on the Clean Air Act Amendments list have relatively abundant data on concentrations; some have virtually none. When concentration data are available, they are more likely to be from ambient-air monitoring or, at best, targeted fixed-point monitoring. For only some of the compounds are sufficient exposure data available for preliminary evaluation of relative priority for more detailed risk assessment (see Appendix A). That is a major problem that can be solved only by a much more extensive state or federal monitoring program. Some states, such as California, are moving rapidly in developing a hazardous air-pollutant monitoring program. Coordination between states and with federal agencies is necessary to keep scarce resources from being wasted in duplicative efforts.

Collection of new exposure data on humans is limited by current methods of monitoring individual exposures (which are often expensive, often of low accuracy or precision, and often nonquantitative or lacking in the ability to determine the source of exposure) and by methods of obtaining information on human behavior that might affect uptake or exposures. In addition, no reference database is available for comparing new data, that is, for determining whether new data represent exposure outside the general norm or are within the realm of acceptability defined by prior studies. Furthermore, when exposure data are gathered, they should be probability-based to allow inferences to the population and estimation of the tails of the distribution of exposures.

Toxicity

A full assessment of the inherent toxicity of an agent requires some combination of structure-activity analyses, in vitro or whole-animal short-term tests, chronic or long-term animal bioassays, human biomonitoring, clinical studies, and epidemiological investigations (NRC, 1984, 1991c,d). A complete hazard identification might entail review of information in all those categories before a determination that a quantitative risk assessment of the agent is warranted (Bailar et al., 1993).

Estimation of dose-effect relationships requires data on the effects of a wide range of doses, on factors that influence the dose delivered to critical target cells by given magnitudes and patterns of exposure (e.g., uptake, anatomic distribution, metabolism, and excretion) (NRC, 1987), on the shapes and slopes of pertinent dose-effect curves, on the relevant mechanisms of effects (NRC, 1991c),

and on the extent to which the response to an agent can vary with species, sex, age, previous exposure, health status, exposure to extraneous agents, and other variables (NRC, 1988a).

Priorities for Collecting Data

Strategies to fill data gaps in toxicity assessment are best developed case by case, but the following priority-setting of the major types of toxicological data that may be used are listed below. In the suggested iterative data-collection process, the toxicity data listed in the first three categories below (i.e., generic and acute toxicity, acute mammalian lethality) should be collected on every chemical as a starting point, and other, more expensive, data should be collected only on chemicals that give cause for concern based on the data in those categories.

1. Generic toxicity data (structure-activity relationships and results of other correlational analyses).
2. Data on acute toxicity (on lethality in microorganisms or effects on mammalian cells in vitro).
3. Acute mammalian lethality data (usually rodent).
4. Toxicokinetics data, phase 1 (on uptake, distribution, retention, and excretion in rodents).
5. Genotoxicity data (results of short-term in vitro tests in microorganisms, *Drosophila*, and mammalian cells).
6. Data on subchronic toxicity (on 14-day or 28-day inhalation toxicity in rodents).
7. Toxicokinetic data, phase 2 (on metabolic pathways and metabolic fate in rodents and other mammalian species, with special attention given to exposure by inhalation).
8. Data on chronic toxicity (on carcinogenicity, neurobehavioral toxicity, reproductive and developmental toxicity, and immunotoxicity in two rodent species of both sexes, with special attention given to the exposure by inhalation).
9. Human toxicity data (clinical, biomonitoring, and epidemiological data).
10. Data on toxic mechanisms, dose-effect relationships, influence of modifying factors (age, sex, and other variables) on susceptibility, and interactive effects of mixtures of chemical and physical agents.

This prioritization is based on the cost and complexity of gathering such data (NRC, 1984). It is generally not possible to plan the collection of clinical and epidemiological data. Toxicological studies conducted clinically in humans are usually planned and implemented under experimental control, but very few are done, because of the attendant hazards. Epidemiological studies are relatively

expensive and often produce data that are difficult to interpret as to effects of specific toxic agents. If one were to set data-collection priorities without concern for cost, ethical, or other considerations, the sequence of collection might be

1. Toxicological human data.
2. Clinical data.
3. Epidemiological data.

Data Availability

Availability of requisite data varies widely among the 189 chemicals. On the one hand, some preliminary toxicity data are available on some of the chemicals, or at least can be estimated from structure-activity correlations. On the other hand, the toxicity data are incomplete on almost all 189 chemicals.

The amount of data available is highly variable and depends largely on the existence of uncontrollable chance events. Generally, better data sets exist on individual chemicals that have been used over long periods (vinyl chloride, some solvents, etc.) and on chemicals of wide use (such as pesticides) than on chemicals rarely used or chemicals that are byproducts of other chemicals (e.g., chemicals in automobile exhaust and cigarette smoke). Additional information and analysis on the Integrated Risk Information System (IRIS) used by EPA is provided in Chapter 12. Some of the partial data needed to test models are discussed in Chapter 6.

Overall Priority Setting

The data needed for each step of risk assessment are summarized in rough order of increasing complexity (see Table 8-2). In an iterative data-collection process, if information in the top one or two items of each of the four columns in Table 8-2 does not indicate increased risk potential the priority for full risk assessment should be low. Various combinations of negative information in the first few items of any two of the first three lists (e.g., emissions, environmental fate and transport, exposure) with positive information in the third list might lead to a medium priority. Positive information in the early items of two, or perhaps three, of the lists would argue for a high priority. Data for the more complex items of each list would be developed when evidence of potential hazard exceeded an agreed-on "bright line" of concern, i.e., a decision point set either by regulation or programmatic procedures.

Although a full priority scheme probably should be on a continuous scale, several important points to develop a more detailed scheme might appear as follows:

TABLE 8-2 Types of Data Available for Risk Assessment

Emissions	Environmental Fate and Transport	Exposure	Toxicity
1. Material balance	1. Physical properties	1. Ambient fixed-point monitoring	1. Generic toxicity
2. Industry-wide emission factors	2. Physicochemical properties of environment	2. Targeted fixed-point monitoring	2. Acute toxicity (lethality for microorganisms or mammalian cells in vitro)
3. Plant-specific emission factors (EPA protocol)	3. Chemical properties or reactivity	3. Duration and frequency of peak concentrations for populations at risk	3. Acute mammalian lethality (rodent)
4. Facility measurements, including flux determinations	4. Rates of potential removal processes	4. Personnel monitoring for average and maximally exposed people	4. Toxicokinetics, phase 1
		5. Biologic markers	5. Genotoxicity (short-term in vitro tests in micro-organisms, *Drosophila* , or mammalian cells)
			6. Subchronic (13-day or 28-day) inhalation toxicity (rodent)
			7. Toxicokinetics, phase 2
			8. Chronic toxicity: carcinogenicity, neurobehavioral toxicity, reproductive and developmental toxicity, or immunotoxicity
			9. Human toxicity (clinical, biomonitoring, epidemiologic)
			10. Toxic mechanisms and dose-effect relationships

Screening risk assessment

Emissions—Items 1 and 2
Environmental fate and transport—Items 1-3
Exposure—Items 1-3
Toxicity—Items 1-3

- If the information for all the above items (or items lower on the list, if available) indicates no potential health concerns, assign "low priority."
- If any information on exposure (emissions, environmental fate and transport, exposure) is positive, assign the chemical "medium priority."
- If any information on exposure is positive (i.e., emission, environmental fate and transport, or exposure measurement), *and* toxicity data are positive, then assign the chemical "high priority" and proceed to the full-scale risk assessment.

Full risk assessment

Emissions—Items 1-4
Environmental fate and transport—Items 1-5
Exposure—Items 1-5
Toxicity—Items 1-10

- If the information is not positive for the higher-order items in all four lists, assign the chemical to Action Level 2 (more extended time response).
- If the information is positive for the high-order items in all four lists, assign the chemical to Action Level 1 (short time-frame response).

Reliable positive human evidence will always result in a high priority and the full risk evaluation. Any positive clinical, toxicologic, or epidemiological human data would override a priority based on exposure and animal toxicity data alone and move a given chemical to the stage of full risk assessment.

The detailed nature of the process used to set priorities for full risk assessment needs to be addressed in a coordinated way by federal and state agencies, to ensure the best use of limited resources for this programmatic step. There might be, for example, a numerical weighting or scoring approach based on data in the four categories of emissions, environmental fate and transport, exposure, and toxicological data. EPA should consider convening a panel of experts to develop a priority-setting process and the requisite accompanying iterative approach to data collection.

Data Management

More attention needs to be paid to data management to ensure that vital data gaps are filled, that data used in risk assessments are of the best possible quality, and that relevant information (such as negative epidemiological information) is

not overlooked. The lack of a consistent data-collection scheme makes data analysis, and thus effective risk assessment, inconsistent and unreliable for risk-management purposes.

For example, risk assessment often requires that the assessor decide whether to set aside information from old studies when newer, supposedly better information is available. The ultimate desire is for credibility; therefore, it is important to use information that is widely acknowledged as the best representation of reality. If the results of a new study contradict information from an old study and if there is only a small difference in the "bottom-line" estimate of human health risk, then both should be used, and the error bounds of the current risk assessment should be revised. However, if the studies lead to quite different conclusions, use of both might be feasible. For example, some animal evidence might show a major health hazard while there may also be weak, negative, or equivocal animal studies. Such conflicting data should be carefully reviewed in the risk-assessment document, with detailed study of possible reasons for the discrepancy. When no reconciliation of results seems feasible, the committee recommends that the voice of prudence be heard and that the risk assessment be either based on the higher ultimate risk estimate or delayed (as was done in part on formaldehyde) until additional studies can be completed.

Findings And Recommendations

The committee's findings and recommendations follow.

Insufficient Data for Risk Assessment

EPA does not have sufficient data to assess fully the health risks of the 189 chemicals in Title III within the time permitted by the Clean Air Act Amendments of 1990.

- EPA should screen the 189 chemicals for priorities for the assessment of health risks, identify the data gaps, and develop incentives to expedite generation of the needed data by other public agencies (such as the National Toxicology Program, the Agency for Toxic Substances and Disease Registry, and state agencies) and by other organizations (industry, academia, etc.).

Need for Data-Gathering Guidelines

EPA has not defined the guidelines or process to be used for determining the types, quantities, and quality of data that are needed for conducting risk assessments for facilities emitting one or more of the 189 chemicals.

- EPA should develop an iterative approach to gathering and evaluating data in the categories of emission, transport and fate, exposure, and toxicology

for use in both screening and full risk assessment. The data-gathering and data-evaluation process should be set forth by EPA in guidelines for use by those who conduct data-gathering activities. To develop these guidelines, EPA should convene a panel of experts to develop a priority-setting scheme that uses a numerical weighting or scoring approach.

Inadequacy of Emission and Exposure Data

EPA has often relied on non-site-specific emission and exposure data. These data are often not sufficient to assess the risk to individuals and the affected population at large.

- EPA should expand its efforts to gather emission and exposure data to personal monitoring and site-specific monitoring.

Inadequacy of TRI Database as a Source of Emission Data for Risk-Assessment Purposes

The SARA 313 Toxic Release Inventory data and other readily available data used by EPA for emission characterization may be adequate for screening purposes but are not adequate for developing detailed risk assessments for specific facilities. Present processes of gathering emission data do not yield information appropriate for all risk-assessment purposes under the Clean Air Act Amendments.

- EPA should modify its data-gathering activities related to emissions to ensure that it has or will acquire the data needed to conduct screening and full risk assessments, especially of the 189 chemicals listed in CAAA-90.

Lack of Adequate Natural Background-Exposure Database

EPA does not have an adequate database on natural background exposures to the 189 air pollutants against which to evaluate total human exposure data from facilities producing or using these substances.

- EPA should develop an ambient-outdoor-exposure database on the 189 listed hazardous air pollutants.

Inadequate Explanation of Analytical Techniques

EPA does not always explain adequately the analytical and measurement methods it uses for estimating ambient outdoor exposures.

- EPA should collate and explain the analytical and measurement methods it uses for ambient outdoor exposures, including the errors, precision, accuracy, detection limits, etc., of all methods that it uses for risk-assessment purposes.

Need for System of Data Management for Risk Assessment

EPA needs more adequate mechanisms to compile and maintain databases for use in health-risk screening and assessment.

- EPA should review its data-management systems and improve them as needed to ensure that the quality and quantity of the data are routinely updated and that the data are sufficiently accessible for risk screening and risk assessment. Its responsibilities under CAAA-90 should be prominent in this review and revision.

9

Uncertainty

The need to confront uncertainty in risk assessment has changed little since the 1983 NRC report *Risk Assessment in the Federal Government.* That report found that:

> The dominant analytic difficulty [in decision-making based on risk assessments] is pervasive uncertainty. … there is often great uncertainty in estimates or the types, probability, and magnitude of health effects associated with a chemical agent of the economic effects of a proposed regulatory action, and of the extent of current and possible future human exposures. These problems have no immediate solutions, given the many gaps in our understanding of the causal mechanisms of carcinogenesis and other health effects and in our ability to ascertain the nature or extent of the effects associated with specific exposures.

Those gaps in our knowledge remain, and yield only with difficulty to new scientific findings. But a powerful solution exists to some of the difficulties caused by the gaps: the systematic analysis of the sources, nature, and implications of the uncertainties they create.

Context Of Uncertainty Analysis

EPA decision-makers have long recognized the usefulness of uncertainty analysis. As indicated by former EPA Administrator William Ruckelshaus (1984):

> First, we must insist on risk calculations being expressed as distributions of estimates and not as magic numbers that can be manipulated without regard to

> what they really mean. We must try to display more realistic estimates of risk to show a range of probabilities. To help do this, we need new tools for quantifying and ordering sources of uncertainty and for putting them into perspective.

Ten years later, however, EPA has made little headway in replacing a risk-assessment "culture" based on "magic numbers" with one based on information about the range of risk values consistent with our current knowledge and lack thereof.

As we discuss in more depth in Chapter 5, EPA has been skeptical about the usefulness of uncertainty analysis. For example, in its guidance to those conducting risk assessments for Superfund sites (EPA, 1991f), the agency concludes that quantitative uncertainty assessment is usually not practical or necessary for site risk assessments. The same guidance questions the value and accuracy of assessments of the uncertainty, suggesting that such analyses are too data-intensive and "can lead one into a false sense of certainty."

In direct contrast, the committee believes that uncertainty analysis is the only way to combat the "false sense of certainty," which is *caused* by a refusal to acknowledge and (attempt to) quantify the uncertainty in risk predictions.

This chapter first discusses some of the tools that can be used to quantify uncertainty. The remaining sections discuss specific concerns about EPA's current practices, suggest alternatives, and present the committee's recommendations about how EPA should handle uncertainty analysis in the future.

Nature Of Uncertainty

Uncertainty can be defined as a lack of precise knowledge as to what the truth is, whether qualitative or quantitative. That lack of knowledge creates an intellectual problem—that we do not know what the "scientific truth" is; and a practical problem—we need to determine how to assess and deal with risk in light of that uncertainty. This chapter focuses on the practical problem, which the 1983 report did not shed much light on and which EPA has only recently begun to address in any specific way. This chapter takes the view that uncertainty is always with us and that it is crucial to learn how to conduct risk assessment in the face of it. Scientific truth is always somewhat uncertain and is subject to revision as new understanding develops, but the uncertainty in quantitative health risk assessment might be uniquely large, relative to other science-policy areas, and it requires special attention by risk analysts. These analysts need to allow questions such as: What should we do in the face of uncertainty? How should it be identified and managed in a risk assessment? How should an understanding of uncertainty be forwarded to risk managers, and to the public? EPA has recognized the need for more and better uncertainty assessment (see EPA memorandum in Appendix B), and other investigators have begun to make substantial progress with the difficult computations that are often required (Monte Carlo

methods, etc.). However, it appears that these changes have not yet affected the day-to-day work of EPA.

Some scientists, mirroring the concerns expressed by EPA, are reluctant to quantify uncertainty. There is concern that uncertainty analysis could reduce confidence in a risk assessment. However, that attitude toward uncertainty may be misguided. The very heart of risk assessment is the responsibility to use whatever information is at hand or can be generated to produce a number, a range, a probability distribution—whatever expresses best the present state of knowledge about the effects of some hazard in some specified setting. Simply to ignore the uncertainty in any process is almost sure to leave critical parts of the process incompletely examined, and hence to increase the probability of generating a risk estimate that is incorrect, incomplete, or misleading.

For example, past analyses of the uncertainty about the carcinogenic potency of saccharin showed that potency estimates could vary by a factor as large as 10^{10}. However, this example is not representative of the ranges in potency estimates when appropriate models are compared. Potency estimates can vary by a factor of 10^{10} only if one allows the choice of some models that are generally recognized as having no biological plausibility and only if one uses those models for a very large extrapolation from high to low doses. The judicious application of concepts of plausibility and parsimony can eliminate some clearly inappropriate models and leave a large but perhaps a less daunting range of uncertainties. What is important, in this context of enormous uncertainty, is not the best estimate or even the ends of this 10^{10}-fold range, but the best-informed estimate of the likelihood that the true value is in a region where one rather than or another remedial action (or none) is appropriate. Is there a small chance that the true risk is as large as 10^{-2}, and what would be the risk-management implications of this very small probability of very large harm? Questions such as these are what uncertainty analysis is largely about. Improvements in the understanding of methods for uncertainty analysis—as well as advances in toxicology, pharmacokinetics, and exposure assessment—now allow uncertainty analysis to provide a much more accurate, and perhaps less daunting, picture of what we know and do not know than in the past.

Taxonomies

Before discussing the practical applications of uncertainty analysis, it may be best to step back and discuss it as an intellectual endeavor. The problem of uncertainty in risk assessment is large, complex, and nearly intractable, unless it is divided into smaller and more manageable topics. One way to do so, as seen in Table 9-1 (Bogen, 1990a), is to classify sources of uncertainty according to the step in the risk assessment process in which they occur. A more abstract and generalized approach preferred by some scientists is to partition all uncertainties into the three categories of bias, randomness, and true variability. This method

TABLE 9-1 Some Generic Sources of Uncertainty in Risk Assessment

I. HAZARD IDENTIFICATION
Unidentified hazards
Definition of incidence of an outcome in a given study (positive-negative association of incidence with exposure)
Different study results
Different study qualities
— conduct
— definition of control population
— physical-chemical similarity of chemical studied to that of concern
Different study types
— prospective, case-control, bioassay, in vivo screen, in vitro screen
— test species, strain, sex, system
— exposure route, duration
Extrapolation of available evidence to target human population
II. DOSE-RESPONSE ASSESSMENT
Extrapolation of tested doses to human doses
Definition of "positive responses" in a given study
— independent vs. joint events
— continuous vs. dichotomous input response data
Parameter estimation
Different dose-response sets
— results
— qualities
— types
Model selection for low-dose risk extrapolation
— low-dose functional behavior of dose-response relationship (threshold, sublinear, linear, supralinear, flexible)
— role of time (dose frequency, rate, duration; age at exposure; fraction of lifetime exposed)
— pharmacokinetic model of effective dose as a function of applied dose
— impact of competing risks

III. EXPOSURE ASSESSMENT	
Contamination-scenario characterization (production, distribution, domestic and industrial storage and use, disposal, environmental transport, transformation and decay, geographic bounds, temporal bounds)	
—	environmental-fate model selection (structural error)
—	parameter estimation error
—	field measurement error
Exposure-scenario characterization	
—	exposure-route identification (dermal, respiratory, dietary)
—	exposure-dynamics model (absorption, intake processes)
Target-population identification	
—	potentially exposed populations
—	population stability over time
Integrated exposure profile	
IV. RISK CHARACTERIZATION	
Component uncertainties	
—	hazard identification
—	dose-response assessment
—	exposure assessment

SOURCE: Adapted from Bogen, 1990a.

of classifying uncertainty is used by some research methodologists, because it provides a complete partition of types of uncertainty, and it might be more productive intellectually: bias is almost entirely a product of study design and performance; randomness a problem of sample size and measurement imprecision; and variability a matter for study by risk assessors but for resolution in risk management (see Chapter 10).

However, a third approach to categorizing uncertainty may be more practical than this scheme, and yet less peculiar to environmental risk assessment than the taxonomy in Table 9-1.

This third approach, a version of which can be found in EPA's new exposure guidelines (EPA, 1992a) and in the general literature on risk assessment uncertainty (Finkel, 1990; Morgan and Henrion, 1990), is adopted here to facilitate communication and understanding in light of present EPA practice. Although the committee makes no formal recommendation on which taxonomy to use, EPA staff might want to consider the alternative classification above (bias,

randomness, and variability) to supplement their current approach in future documents. Our preferred taxonomy consists of:

- *Parameter uncertainty*. Uncertainties in parameter estimates stem from a variety of sources. Some uncertainties arise from measurement errors; these in turn can involve random errors in analytic devices (e.g., the imprecision of continuous monitors that measure stack emissions) or systematic biases (e.g., measuring inhalation from indoor ambient air without considering the effect of volatilization of contaminants from hot water used in showering). A second type of parameter uncertainty arises when generic or surrogate data are used instead of analyzing the desired parameter directly (e.g., the use of standard emission factors for industrialized processes). Other potential sources of error in estimates of parameters are misclassification (e.g., incorrect assignment of exposures of subjects in historical epidemiological studies due to faulty or ambiguous information), random sampling error (e.g., estimation of risk to laboratory animals or exposed workers from outcomes observed in only a small sample), and nonrepresentativeness (e.g., developing emission factors for dry cleaners based on a sample that included predominantly "dirty" plants due to some quirk in the study design).[1]
- *Model uncertainty*. These uncertainties arise because of gaps in the scientific theory that is required to make predictions on the basis of causal inferences. For example, the central controversy over the validity of the linear, no threshold model for carcinogen dose-response is an argument over model uncertainty. Common types of model uncertainties include relationship errors (e.g., incorrectly inferring the basis for correlations between chemical structure and biologic activity) and errors introduced by oversimplified representations of reality (e.g., representing a three-dimensional aquifer with a two-dimensional mathematical model). Moreover, any model can be incomplete if it excludes one or more relevant variables (e.g., relating asbestos to lung cancer without considering the effect of smoking on both those exposed to asbestos and those unexposed), uses surrogate variables for ones that cannot be measured (e.g., using wind speed at the nearest airport as a proxy for wind speed at the facility site), or fails to account for correlations that cause seemingly unrelated events to occur much more frequently than would be expected by chance (e.g., two separate components of a nuclear plant are both missing a particular washer because the same newly hired assembler put both of them together). Another example of model uncertainty concerns the extent of aggregation used in the model. For example, to fit data on the exhalation of volatile compounds adequately in physiologically based pharmacokinetic (PBPK) models, it is sometimes necessary to break up the fat compartment into separate compartments reflecting subcutaneous and abdominal fat (Fiserova-Bergerova, 1992). In the absence of enough data to indicate the inadequacy of using a single aggregated variable (total body fat), the modeler might construct an unreliable model. The uncertainty in risk

that results from uncertainty about models might be as high as a factor of 1,000 or even greater, even if the same data are used to determine the results from each. This can occur, for example, when the analyst must choose between a linear multistage model and a threshold model for cancer dose-response relations.

Problems With EPA's Current Approach To Uncertainty

EPA's current practice on uncertainty is described elsewhere in this report, especially in Chapter 5, as part of the risk-characterization process. Overall, EPA tends at best to take a qualitative approach to uncertainty analysis, and one that emphasizes model uncertainty rather than parameter uncertainties. The uncertainties in the models and the assumptions made are listed (or perhaps described in a narrative way) in each step of the process; these are then presented in a nonquantitative statement to the decision-maker.

Quantitative uncertainty analysis is not well explored at EPA. There is little internal guidance for EPA staff about how to evaluate and express uncertainty. One useful exception is the analysis conducted for the National Emission Standards for Hazardous Air Pollutants (NESHAPS) radionuclides document (described in Chapter 5), which provides a good initial example of how uncertainty analysis could be conducted for the exposure portion of risk assessment. Other EPA efforts, however, have been primarily qualitative, rather than quantitative. When uncertainty is analyzed at EPA, the analysis tends to be piecemeal and highly focused on the sensitivity of the assessment to the accuracy of a few specified assumptions, rather than a full exploration of the process from data collection to final risk assessment, and the results are not used in a systematic fashion to help decision-makers.

The major difficulty with EPA's current approach is that it does not supplant or supplement artificially precise single estimates of risk ("point estimates") with ranges of values or quantitative descriptions of uncertainty, and that it often lacks even qualitative statements of uncertainty. This obscures the uncertainties inherent in risk estimation (Paustenbach, 1989; Finkel, 1990), although the uncertainties themselves do not go away. Risk assessments that do not include sufficient attention to uncertainty are vulnerable to four common and potentially serious pitfalls (adapted from Finkel, 1990):

1. They do not allow for optimal weighing of the probabilities and consequences of error for policy-makers so that informed risk-management decisions can be made. An adequate risk characterization will clarify the extent of uncertainty in the estimates so that better-informed choices can be made.
2. They do not permit a reliable comparison of alternative decisions, so that appropriate priorities can be established by policy-makers comparing several different risks.

3. They fail to communicate to decision-makers and the public the range of control options that would be compatible with different assessments of the true state of nature. This makes informed dialogue between assessors and stakeholders less likely, and can cause erosion of credibility as stakeholders react to the overconfidence inherent in risk assessments that produce only point estimates.
4. They preclude the opportunity for identifying research initiatives that might reduce uncertainty and thereby reduce the probability or the impact of being caught by surprise.

Perhaps most fundamentally, without uncertainty analysis it can be quite difficult to determine the conservatism of an estimate. In an ideal risk assessment, a complete uncertainty analysis would provide a risk manager with the ability to estimate risk for each person in a given population in both actual and projected scenarios of exposures; it would also estimate the uncertainty in each prediction in quantitative, probabilistic terms. But even a less exhaustive treatment of uncertainty will serve a very important purpose: it can reveal whether the point estimate used to summarize the uncertain risk is "conservative," and if so, to what extent. Although the choice of the "level of conservatism" is a risk-management prerogative, managers might be operating in the dark about how "conservative" these choices are if the uncertainty (and hence the degree to which the risk estimate used may fall above or below the true value) is ignored or assumed, rather than calculated.

Some Alternatives To EPA's Approach

A useful alternative to EPA's current approach is to set as a goal a quantitative assessment of uncertainty. Table 9-2, from Resources for the Future's Center for Risk Management, suggests a sequence of steps that the agency could follow to generate a quantitative uncertainty estimate. To determine the uncertainty in the estimate of risk associated with a source probably requires an understanding of the uncertainty in each of the elements shown in Table 9-3. The following pages describe more fully the development of probabilities and the method of using probabilities as inputs into uncertainty analysis models.

Probability Distributions

A probability density function (PDF) describes the uncertainty, encompassing objective or subjective probability, or both, over all possible values of risk. When the PDF is presented as a smooth curve, the area under the curve between any two points is the probability that the true value lies between the two points. A cumulative distribution function (CDF), which is the integral or sum of the PDF up to each point, shows the probability that a variable is equal to or less than each of the possible values it can take on. These distributions can sometimes

TABLE 9-2 Steps That Could Improve a Quantitative Uncertainty Estimate

1. *Determine the desired measure of risk* (e.g., mortality, life years lost, risk to the individual who is maximally exposed, number of persons at more than arbitrary "unacceptable" risk.) More than one measure will often be desired, but the remaining steps will need to be followed *de novo* for each method.
2. *Specify one or more "risk equations," mathematical relationships that express the risk measure in terms of its components*. For example, $R = C \times I \times P$ (risk equals concentration times intake times potency) is a simple "risk equation" with three independent variables. Care must be taken to avoid both an excess and an insufficiency of detail.
3. *Generate an uncertainty distribution for each component.* This will generally involve the use of analogy, the use of statistical inference, of expert opinion, or a combination of these.
4. *Combine the individual distributions into a composite uncertainty distribution.* This step will often require Monte Carlo simulation (described later).
5. *"Recalibrate" the uncertainty distributions.* At this point, inferential analysis should enter or re-enter the process to corroborate or correct the outputs of step 4. In practice, it might involve altering the range of the distribution to account for dependence among the variables or truncating the distributions to exclude extreme values that are physically or logically impossible. Repeat steps 3, 4, and 5 as needed.
6. *Summarize the output, highlighting important implications for risk management*. Here the decision-maker and uncertainty analyst need to work together (or at least to understand each other's needs and limitations). In all written and oral presentations, the analyst should strive to ensure that the manager understands the following four aspects of the results:
   - Their implications for supplanting any point estimate that might have been produced without consideration of uncertainty. In particular, presentations of uncertainty will help in advancing the debate over whether the standardized procedures used to generate point estimates of risk are too "conservative" in general or particular cases.
   - Their insights regarding the balance between the costs of overestimating and underestimating risk (i.e., the shape and breadth of the uncertainty distribution informs the manager about how prudent various risk estimates might be).
   - Their sensitivity to fundamentally unresolved scientific controversies.
   - Their implications for research, identifying which uncertainties are most important and which uncertainties are amenable to reduction by directed research efforts. As part of this process, the analyst should attempt to quantify in absolute terms how much total effort might be put into reducing uncertainty before a control action is implemented (i.e., estimate the value of information using standard techniques).

SOURCE: Adapted from Finkel, 1990.

be estimated empirically with statistical techniques that can analyze large sets of data adequately. Sometimes, especially when data are sparse, a normal or lognormal distribution is assumed and its mean and variance (or standard deviation) are estimated from available data. When data are in fact normally distributed over the whole range of possible values, the mean and variance completely characterize the distribution, including the PDF and CDF. Thus, with certain assumptions (such as normality), only a few points might be needed to estimate the whole distribution for a given variable, although more points will both improve

TABLE 9-3 Some Key Variables in Risk Assessment for Which Probability Distributions Might Be Needed

Model Component	Output Variable	Independent Parameter Variable
Transport	Air concentration	Chemical emission rate Stack exit temperature Stack exit velocity Mixing heights
Deposition	Deposition rate	Dry-deposition velocity Wet-deposition velocity Fraction of time with rain
Overland	Surface-water load	Fraction of chemical in overload runoff
Water	Surface-water concentration	River discharge Chemical decay coefficient in river
Soil	Surface-soil concentration	Surface-soil depth Exposure duration Exposure period Cation exchange capacity Decay coefficient in soil
Food Chain	Plant concentration	Plant interception fraction Weathering elimination rate Crop density Soil-to-plant bioconcentration factor
	Fish concentration	Water-to-fish bioconcentration factor
Dose	Inhalation dose	Inhalation rate Body weight
	Ingestion dose	Plant ingestion rate Soil ingestion rate Body weight
	Dermal-absorption dose	Exposed skin surface area Soil absorption factor Exposure frequency Body weight
Risk	Total carcinogenic risk	Inhalation carcinogenic potency factor Ingestion carcinogenic potency factor Dermal-absorption carcinogenic potency factor

SOURCE: Adapted from Seigneur et al., 1992.

the representation of the uncertainty and allow examination of the normality assumption. However, the problem remains that apparently minor deviations in the extreme tails may have major implications for risk assessment (Finkel, 1990). Furthermore, it is important to note that the assumption of normality may be inappropriate.

When data are flawed or not available or when the scientific base is not understood well enough to quantify the probability distributions of all input variables, a surrogate estimate of one or more distributions can be based on analysis of the uncertainty in similar variables in similar situations. For example, one can approximate the uncertainty in the carcinogenic potency of an untested chemical by using the existing frequency distribution of potencies for chemicals already tested (Fiering et al., 1984).

Subjective Probability Distributions

A different method of probability assessment is based on expert opinion. In this method, the beliefs of selected experts are elicited and combined to provide a subjective probability distribution. This procedure can be used to estimate the uncertainty in a parameter (cf., the subjective assessment of the slope of the dose-response relationship for lead in Whitfield and Wallsten, 1989). However, subjective assessments are more often used for a risk assessment component for which the available inference options are logically or reasonably limited to a finite set of identifiable, plausible, and often mutually exclusive alternatives (i.e., for *model* uncertainty). In such an analysis, alternative scenarios or models are assigned subjective probability weights according to the best available data and scientific judgment; equal weights might be used in the absence of reliable data or theoretical justifications supporting any option over any other. For example, this approach could be used to determine how much the risk assessor should rely on relative surface area vs. body weight in conducting a dose-response assessment. The application of particular sets of subjective probability weights in particular inference contexts could be standardized, codified, and updated as part of EPA's implementation of uncertainty analysis guidelines (see below).

Objective probabilities might seem inherently more accurate than subjective probabilities, but this is not always true. Formal methods (Bayesian statistics)[2] exist to incorporate objective information into a subjective probability distribution that reflects other matters that might be relevant but difficult to quantify, such as knowledge about chemical structure, expectations of the effects of concurrent exposure (synergy), or the scope of plausible variations in exposure. The chief advantage of an objective probability distribution is, of course, its objectivity; right or wrong, it is less likely to be susceptible to major and perhaps undetectable bias on the part of the analyst; this has palpable benefits in defending a risk assessment and the decisions that follow. A second advantage is that objective

probability distributions are usually far easier to determine. However, there can be no rule that objective probability estimates are always preferred to subjective estimates, or vice versa.

Model Uncertainty: "Unconditional" Versus "Conditional" PDFs

Regardless of whether objective or subjective methods are used to assess them, the distinction between parameter uncertainty and model uncertainty remains pivotal and has implications for implementing improved risk assessments that acknowledge uncertainty. The most important difference between parameter uncertainty and model uncertainty, especially in the context of risk assessment, concerns how to interpret the output of an objective or subjective probability assessment for each.

One can readily construct a probability distribution for risk, exposure, potency, or some other quantity that reflects the probabilities that various values, corresponding to fundamentally different scientific models, represent the true state. Such a depiction, which we will call an "unconditional PDF" because it tries to represent all the uncertainty surrounding the quantity, can be useful for some decisions that agencies must make. In particular, EPA's research offices might be able to make more efficient decisions about where resources should be channeled to study particular risks, if the uncertainty in each risk were presented unconditionally. For example, an unconditional distribution might be reported in this way: "the potency of chemical X is 10^{-2} per part per million of air (with an uncertainty of a factor of 5 due to parameter uncertainty surrounding this value), but only if the LMS model is correct; if instead the chemical has a threshold, the potency at any ambient concentration is effectively zero." It might even help to assign subjective weights to the current thinking about the probability that each model is correct, especially if research decisions have to be made for many risks.

In addition, some specified *regulatory* decisions—those involving the ranking of different risks for the purpose of allowing "tradeoffs" or "offsets"—can also suffer if model uncertainty is not quantified. For example, two chemicals (Y and Z) with the same potency—assuming that the LMS model is correct—might involve different degrees of confidence in the veracity of that model assumption. If we judged that chemical Y had a 90%, or even a 20%, chance of acting in a threshold fashion, it might be a mistake to treat it as having the same potency as a chemical Z that is virtually certain to have no threshold and then to allow increased emissions of Z in exchange for greater reductions in Y.

However, unconditional statements of uncertainty can be misleading if managers use them for standard-setting, residual-risk decisions, or risk communication, and especially if others then misinterpret these statements. Consider two situations, involving the same hypothetical chemical, in which the same amount of uncertainty can have different implications, depending on whether it stems

from parameter uncertainty (Situation A) or ignorance about model choice (Situation B). In Situation A, suppose that the uncertainty is due entirely to parameter sampling error in a single available bioassay involving few test animals. If 3 of 30 mice tested in that bioassay developed tumors, then a reasonable central-tendency estimate of the risk to mice at the dose used would be 0.1 (3/30). However, because of sampling error, there is approximately a 5% probability that the true number of tumors might be as low as zero (leading to zero as the lower confidence limit, LCL, of risk) and about a 5% probability that the true number of tumors is 6 or higher (leading to 0.2 (6/30) as the upper confidence limit, UCL, of risk).

In Situation B, suppose instead that the uncertainty is due entirely to ambiguity over which model of biological effect is correct. In this hypothetical situation, there was one bioassay in which 200 of 1,000 mice developed tumors; the risk to mice at the dose would be 0.2 (with essentially no parameter uncertainty due to the very large sample size). But suppose scientists disagree about whether the effect in mice is at all relevant to humans, because of profound metabolic or other differences between the two species, but can agree to assign equal probabilities of 50% to each eventuality. In this case as well, the LCL of the risk to humans would be zero (if the "nonrelevance" theory were correct), and the UCL would be 0.2 (if the "relevance" theory were correct), and it would be tempting to report a "central estimate" of 0.1, corresponding to the expected value of the two possible outcomes, weighted by their assigned probabilities. In either situation A or B, it would be *mathematically* correct to say the following: "The expected value of the estimate of the number of annual excess cancer deaths nationwide caused by exposure to this substance is 1,000; the LCL of this estimate is zero deaths, and the UCL is 2,000 deaths."[3]

We contend that in such cases, which typify the two kinds of uncertainties that risk managers must deal with, it would be a mistake simply to report the confidence limits and expected value in Situation B as one might do more routinely in Situation A, especially if one then used these summary statistics to make a regulatory decision. The risk-communication problem in treating this dichotomous model uncertainty (Situation B) as though it were a continuous probability distribution is that it obscures important information about the scientific controversy that must be resolved. Risk managers and the public should be given the opportunity to understand the sources of the controversy, to appreciate why the subjective weights assigned to each model are at their given values, and to judge for themselves what action is appropriate when the two theories, *at least one of which must be incorrect*, predict such disparate outcomes.

More critically, the expected value in Situation B might have dramatically different properties as an estimate for decision-making from the one in Situation A. The estimate of 1,000 deaths in Situation B is a contrivance of multiplying subjective weights that corresponds to no possible true value of risk, although this is not itself a fatal flaw; indeed, it is possible that a strategy of deliberately

inviting errors of both overprotection and underprotection at each decision will turn out to be optimal over a long-run set of similar decisions. The more fundamental problem is that any estimate of central tendency does not necessarily lead to optimal decision-making. This would be true even if society had no desire to make conservative risk management decisions.

Simply put, although classical decision theory does encourage the use of expected values that take account of all sources of uncertainty, it is not in the decision-maker's or society's best interest *to treat fundamentally different predictions as quantities that can be "averaged" without considering the effects of each prediction on the decision that it leads to*. It is possible that a coin-toss gamble between zero deaths and 2,000 deaths would lead a regulator rationally to act as though 1,000 deaths were the certain outcome. But this is only a shorthand description of the actual process of expected-value decision-making, which asks how the *decisions* that correspond to estimates of zero deaths, 1,000 deaths, and 2,000 deaths perform relative to each other, in light of the possibility that each estimate (and hence each decision) is wrong. In other words, the choice to use an unconditional PDF when there is the kind of model uncertainty shown in situation B is a choice between the *possibility* of overprotecting or underprotecting—if one model is accepted and the other rejected—and the *certainty* of erring in one direction or the other if the hybrid estimate of 1,000 is constructed. Because in this example the outcomes are numbers that can be manipulated mathematically, it is tempting to report the average, but this would surely be nonsensical if the outcomes were not numerical. If, for example, there were model uncertainty about where on the Gulf Coast a hurricane would hit, it would be sensible to elicit subjective judgment about the probability that a model predicting that the storm would hit in New Orleans was correct, versus the probability that an alternative model—say, one that predicted that the storm would hit in Tampa—was correct. It would also be sensible to assess the expected losses of lives and property if relief workers were irrevocably deployed in one location and the storm hit the other ("expected" losses in the sense of probability times magnitude). It would be foolish, however, to deploy workers irrevocably in Alabama on the grounds that it was the "expected value" of halfway between New Orleans and Tampa under the model uncertainty—and yet this is just the kind of reasoning invited by indiscriminate use of averages and percentiles from distributions dominated by model uncertainty.

Therefore, we recommend that analysts present *separate* assessments of the parameter uncertainty that remains for *each* independent choice of the underlying model(s) involved. This admonition is not inconsistent with our view that model uncertainty is important and that the ideal uncertainty analysis should consider and report all important uncertainties; we simply suspect that comprehension and decision-making might suffer if all uncertainties are lumped together indiscriminately. The subjective likelihood that each model (and hence each parameter uncertainty distribution) might be correct should still be elicited and

reported, *but primarily to help the decision-maker gauge which depiction of risk and its associated parameter uncertainty is the correct one*, and not to construct a single hybrid distribution (except for particular purposes involving priority-setting, resource allocation, etc.). In the hypothetical Situation B, this would mean presenting both models, their predictions, and their subjective weights, rather than simple summary statistics, such as the unconditional mean and UCL.

The existence of default options for model uncertainty (as discussed in the introduction to Part II and in Chapter 6) also places an important curb on the need for and use of unconditional depictions of uncertainty. If, as we recommend, EPA develops explicit principles for choosing and modifying its default models, it will further codify the practice that for every risk assessment, a sequence of "preferred" model choices will exist, with only one model being the prevailing choice at each inference point where scientific controversy exists. Therefore, the "default risk characterization," including uncertainty, will be the uncertainty distribution (embodying the various sources of parameter and scenario uncertainty) that is conditional on the approved choices for dose-response, exposure, uptake, and other models made under EPA's guidelines and principles. For each risk assessment, this PDF, rather than the single point estimate currently in force, should serve as the quantitative-risk input to standard-setting and residual-risk decisions that EPA will make under the act.

Thus, given the current state of the art and the realities of decision-making, model uncertainty should play only a subsidiary role in risk assessment and characterization, although it might be important when decision-makers integrate all the information necessary to make regulatory decisions. We recognize the intellectual and practical reasons for presenting alternative risk estimates and PDFs corresponding to alternative models that are scientifically plausible, but that have not supplanted a default model chosen by EPA. However, we suggest that to create a single risk estimate or PDF out of various different models not only could undermine the entire notion of having default models that can be set aside for sufficient reason, but could lead to misleading and perhaps meaningless hybrid risk estimates. We have presented this discussion of the pitfalls of combining the results of incompatible models to support our view urging caution in applying these techniques in EPA's risk assessment. Such techniques should not be used for calculating unit risk estimates, because of the potential for misinterpretation of the quantitative risk characterization.[4] However, we encourage risk assessors and risk managers to work closely together to explore the implications of model uncertainty for risk management, and in this context explicit characterization of model uncertainty may be helpful. The characterization of model uncertainty may also be appropriate and useful for risk communication and for setting research priorities.

Finally, an uncertainty analysis that carefully keeps separate the influence of fundamental model uncertainties versus other types of uncertainty can reveal which controversies over model choice are actually important to risk management

and which are "tempests in teapots." If, as might often be the case, the effect of all parameter uncertainties (and variabilities) is as large as or larger than that contributed by the controversy over model choice, then resolving the controversy over model choice would not be a high priority. In other words, if the "signal" to be discerned by a final answer as to which model or inference option is correct is not larger than the "noise" caused by parameter uncertainty in either (all) model (s), then effort should be focused on data collection to reduce the parameter uncertainties, rather than on basic research to resolve the modeling controversies.

Specific Guidance On Uncertainty Analysis

Generating Probability Distributions

The following examples indicate how probability distributions might be developed in practice and illustrate many of the principles and recommended procedures discussed earlier in the chapter.

- *Example 1.* Estimated emission rates can differ significantly from actual values. Experience might show that emission estimates based on emission factors, mass balances, or material balances have an inherent uncertainty of a factor of about 100, whereas those based on testing tend to be within a factor of about 10. Expert opinion and analysis of past studies of such emission estimates could provide more definitive bounds on the estimates and result in a probability distribution. For example, a lognormal distribution with the median at the calculated emission estimate and a geometric standard deviation[5] of 10 (i.e., the case of emission factors) or 10 (for emissions based on testing).
- *Example 2.* A standard animal carcinogenicity bioassay provides the raw material for three related features of a complete uncertainty analysis. First, there is the random sampling uncertainty due to the limitation on the number of animals that can be tested. Suppose that at a particular dose 10 of 50 mice develop leukemia. The most likely estimate of the risk to each mouse would be calculated as 0.2 (the observed risk to the group, 10/50). However, chance dictates that if different groups of 50 animals were exposed to a risk of 0.2, some number *n* other than 10 might develop leukemia at each replication of the experiment. According to the binomial theorem, which governs independent dichotomous chance events (such as a coin falling either "heads" or "tails"), between 4 and 16 animals would develop cancer 99% of the time if many groups of 50 animals were exposed to identical lifetime risks of 0.2. EPA's standard procedure of reporting only the "$q_1{}^*$" value for potency is equivalent to computing the 95th percentile of random uncertainty using the binomial theorem (e.g., assuming that if 10 tumors were observed, 14 tumors would be a "conservative" estimate), and then finding the slope of the straight line drawn between this hypothetical response

and the control-group response. Such a point estimate is informative neither about the plausible slopes greater and less than this value nor about the relative probabilities of the different plausible values. A distribution for q_1 derived from the entire binomial probability distribution for n, on the other hand, would answer both of these concerns.

A second opportunity, which allows the analyst to draw out some of the model uncertainty in dose-response relationships, stems from the flexibility of the LMS model. Even though this model is often viewed as unduly restrictive (e.g., it does not allow for thresholds or for "superlinear" dose-response relations at low doses), it is inherently flexible enough to account for sublinear dose-response relations (e.g., a quadratic function) at low doses. EPA's point-estimation procedure forces the q_1^* value to be associated with a linear low-dose model, but there is no reason why EPA could not fit an unrestricted model through all the values on the binomial uncertainty distribution of tumor response, thereby generating a distribution for potency that might include some probability that the true dose-response function is of quadratic or higher order (see, for example, Guess et al., 1977; Finkel, 1988).

Finally, EPA could account for another source of parameter uncertainty if it made use of more than one data set for each carcinogen. Techniques of meta-analysis, more and more frequently used to generate composite *point estimates* by averaging together the results of different studies (e.g., a second mouse study that might have found 20 leukemic animals out of 50 at the same dose), can perhaps more profitably be used to generate a composite *uncertainty distribution*. This distribution could be broader than the binomial distribution that would arise from considering the sampling uncertainty in a single study, if the new study contradicted the first, or it could be narrower, if the results of each study were reinforcing (i.e., each result was well within the uncertainty range of the other).

- *Example 3.* The linearized multistage (LMS) model is often used to estimate dose-response relationships. Although many models could be used to estimate this relationship, two—the LMS and the biologically motivated (BM) models—seem to have the best biologic and mechanistic underpinning. Others, such as the probit and logit models, do not have a similar underpinning and are generic dose-response models. An additional possible advantage of BM models is their flexibility to accommodate the possibility of zero added response at low doses, even when there is a response at high doses. At present, there is rarely enough information to use BM models with great confidence, and a key issue is the plausibility of no increased hazard at low doses. If available information on such matters as biochemistry, genotoxicity, and induced cell replication suggests that low doses do not increase risk above background levels, then the question arises whether the subjective probability of risk at low doses should include both a positive probability that the risk is zero and a probability distribution for the

degree of potency if it is not zero. In application, that might result in one of the following three decisions:

— If the data are sufficient to use the BM model, specify its parameters, and conclude scientifically (using whatever principles and evidentiary standards EPA sets forth in response to the committee's recommendation that it develop such principles) that this model is appropriate, the BM model could be used. Such occurrences are likely to be uncommon in the near term because of the need for extensive data of special types.

— If the data lead to a scientific conclusion that there is a substantial possibility that the low-dose potency is zero, the potency distributions from the BM and LMS models could be presented separately, perhaps with a narrative or quantitative statement of the probability weights to be assigned to each model.

— If the data do not suggest a substantial possibility of zero risk at low doses, the LMS model would continue to be used exclusively.

Statistical Analysis of Generated Probabilities

Once the needed subjective and objective probability distributions are estimated for each variable in the risk assessment, the estimates can be combined to determine their impact on the ultimate risk characterization. Joint distributions of input variables are often mathematically intractable, so an analyst must use approximating methods, such as numerical integration or Monte Carlo simulation. Such approximating methods can be made arbitrarily precise by appropriate computational methods. Numerical integration replaces the familiar operations of integral calculus by summarizing the values of the dependent variable(s) on a very fine (multivariate) grid of the independent variables. Monte Carlo methods are similar, but sum the variables calculated at random points on the grid; this is especially advantageous when the number or complexity of the input variables is so large that the costs of evaluating all points on a sufficiently fine grid would be prohibitive. (For example, if each of three variables is examined at 100 points in all possible combination, the grid would require evaluation at 100^3 = 1,000,000 points, whereas a Monte Carlo simulation might provide results that are almost as accurate with only 1,000-10,000 randomly selected points.)

Barriers to Quantitative Uncertainty Analysis

The primary barriers to determining objective probabilities are lack of adequate scientific understanding and lack of needed data. Subjective probabilities are also not always available. For example, if the fundamental molecular-biologic bases of some hazards are not well understood, the associated scientific

uncertainties cannot be reasonably characterized. In such a situation, it would be prudent public-health policy to adopt inference options from the conservative end of the spectrum of scientifically plausible available options. Quantitative dose-response assessment, with characterization of the uncertainty in the assessment, could then be conducted conditional on this set of inference options. Such a "conditional risk assessment" could then routinely be combined with an uncertainty analysis for exposure (which might not be subject to fundamental model uncertainty) to yield an estimate of risk and its associated uncertainty.

The committee recognizes the difficulties of using subjective probabilities in regulation. One is that someone would have to provide the probabilities to be used in a regulatory context. A "neutral" expert from within EPA or at a university or research center might not have the knowledge needed to provide a well-informed subjective probability distribution, whereas those who might have the most expertise might have or be perceived to have a conflict of interest, such as persons who work for the regulated source or for a public-interest group that has taken a stand on the matter. Allegations of conflict of interest or lack of knowledge regarding a chemical or issue might damage the credibility of the ultimate product of a subjective assessment. We note, however, that most of the same problems of real or perceived bias pervade EPA's current point-estimation approach.

At bottom, what matters is how risk managers and other end-users of risk assessments interpret the uncertainty in risk analysis. Correct interpretation is often difficult. For example, risks expressed on a logarithmic scale are commonly misinterpreted by assuming that an error of, say, a factor of 10 in one direction balances an error of a factor of 10 in the other. In fact, if a risk is expressed as 10^{-5} within a factor of 100 uncertainty in either direction, the average risk is approximately 1/2,000, rather than 1/100,000. In some senses, this is a problem of risk communication within the risk-assessment profession, rather than with the public.

Uncertainty Guidelines

Contrary to EPA's statement that the quantitative techniques suggested in this chapter "require definition of the distribution of all input parameters and knowledge of the degree of dependence (e.g., covariance) among parameters," (EPA, 1991f) complete knowledge is not necessary for a Monte Carlo or similar approach to uncertainty analysis. In fact, such a statement is a tautology: it is the uncertainty analysis that tells scientists how their lack of "complete knowledge" affects the confidence they can have in their estimate. Although it is always better to be able to be precise about how uncertain one is, an imprecise statement of uncertainty reflects how uncertain the situation is—it is far better to acknowledge this than to respond to the "lack of complete knowledge" by holding fast to a "magic number" that one knows to be wildly overconfident. Uncertainty

analysis simply estimates the logical implications of the assumed model and whatever assumed or empirical inputs the analyst chooses to use.

The difficulty in documenting uncertainty can be reduced by the use of uncertainty guidelines that will provide a structure for how to determine uncertainty for each parameter and for each plausible model. In some cases, objective probabilities are available for use. In others, a subjective consensus about the uncertainty may be based on whatever data are available. Once these decisions are documented, many of the difficulties in determining uncertainty can be alleviated. However, it is important to note that consensus might not be achieved. If a "first-cut" characterization of uncertainty in a specific case is deemed to be inappropriate or superseded by new information, it can be changed by means of such procedures as those outlined in Chapter 12.

The development of uncertainty guidelines is important, because a lack of clear statements as to how to address uncertainty in risk assessment might otherwise lead to continuing inconsistency in the extent to which uncertainty is explicitly considered in assessments done by EPA and other parties, as well as to inconsistencies in how uncertainty is quantified. Developing guidelines to promote consistency in efforts to understand the uncertainty in risk assessment should improve regulatory and public confidence in risk assessment, because guidelines would reduce inappropriate inconsistencies in approach, and where inconsistencies remain, they could help to explain why different federal or state agencies come to different conclusions when they analyze the same data.

Risk Management And Uncertainty Analysis

The most important goal of uncertainty analysis is to improve risk management. Although the process of characterizing the uncertainty in a risk analysis is also subject to debate, it can at a minimum make clear to decision-makers and the public the ramifications of the risk analysis in the context of other public decisions. Uncertainty analysis also allows society to evaluate judgments made by experts when they disagree, an especially important attribute in a democratic society. Furthermore, because problems are not always resolved and analyses often need to be repeated, identification and characterization of the uncertainties can make the repetition easier.

Single Estimates of Risk

Once EPA succeeds in supplanting single point estimates with quantitative descriptions of uncertainty, its risk assessors will still need to summarize these distributions for risk managers (who will continue to use numerical estimates of risk as inputs to decision-making and risk communication). It is therefore crucial to understand that uncertainty analysis is *not* about replacing "risk numbers" with risk distributions or any other less transparent method; it is about *consciously*

selecting the appropriate numerical estimate(s) from out of an understanding of the uncertainty.

Regardless of whether the applicable statute requires the manager to balance uncertain benefits and costs or to determine what level of risk is "acceptable," a bottom-line summary of the risk is a very important input, as it is critical to judging how confident the decision-maker can be that benefits exceed costs, that the residual risk is indeed "acceptable," or whatever other judgments must be made. Such summaries should include at least three types of information: (1) a fractile-based summary statistic, such as the median (the 50th percentile) or a 95th-percentile upper confidence limit, which denotes the probability that the uncertain quantity will fall an unspecified distance above or below some associated value; (2) an estimate of the mean and variance of the distribution, which along with the fractile-based statistic provides crucial information about how the probabilities and the absolute magnitudes of errors interrelate; and (3) a statement of the potential for errors and biases in these estimates of fractiles, mean, and variance, which can stem from ambiguity about the underlying models, approximations introduced to fit the distribution to a standard mathematical form, or both.

One important issue related to uncertainty is the extent to which a risk assessment that generates a point estimate, rather than a range of plausible values, is likely to be too "conservative" (that is, to excessively exaggerate the plausible magnitude of harm that might result from specified environmental exposures). As the two case studies that include uncertainty analysis (Appendixes F and G) illustrate, these investigations can show whether "conservatism" is in fact a problem, and if so, to what extent. Interestingly, the two studies reach opposite conclusions about "conservatism" in their specific risk-assessment situations; perhaps this suggests that facile conclusions about the "conservatism" of risk assessment in general might be off the mark. On the one hand, the study in Appendix G claims that EPA's estimate of MEI risk (approximately 10^{-1}) is in fact quite "conservative," given that the study calculates a "reasonable worst-case risk" to be only about 0.0015.[6] However, we note that this study essentially compared different and incompatible models for the cancer potency of butadiene, so it is impossible to discern what percentile of this unconditional uncertainty distribution any estimate might be assigned (see the discussion of model uncertainty above). On the other hand, the Monte Carlo analysis of parameter uncertainty in exposure and potency in Appendix F claims that EPA's point estimate of risk from the coal-fired power plant was only at the 83rd percentile of the relevant uncertainty distribution. In other words, a standard "conservative" estimate of risk (the 95th percentile) *exceeds* EPA's value, in this case by a factor of 2.5. It also appears from Figure 5-7 in Appendix F that there is about a 1% chance that EPA's estimate is too low by more than a factor of 10. Note that both case studies (Appendixes F and G) fail to distinguish sources of uncertainty from sources of interindividual variability, so the corresponding "uncertainty" distributions obtained cannot be used to properly characterize uncertainty either

in predicted incidence or in predicted risk to some particular (e.g., average, highly exposed, or high-risk) individual (see Chapter 11 and Appendix I-3).

As discussed above, access to the entire PDF allows the decision-maker to assess the amount of "conservatism" implicit in any estimate chosen from the distribution. In cases where the risk manager asks the analyst to summarize the PDF via one or more summary statistics, the committee suggests that EPA might consider a particular kind of point estimate to summarize uncertain risks, in light of the two distinct kinds of "conservatism" discussed in Appendix N-1 (the "level of conservatism," the relative percentile at which the point estimate of risk is located, and the "amount of conservatism," the absolute difference between the point estimate and the mean). Although the specific choice of this estimate should be left to EPA risk managers, and may also need to be flexible enough to accommodate case-specific circumstances, estimates do exist that can account for both the percentile and the relationship to the mean in one single number. For example, EPA could choose to summarize uncertain risks for reporting the mean of the upper five percent of the distribution. It is a mathematical truism that (for right-skewed distributions commonly encountered in risk assessment) the larger the uncertainty, the greater the chance that the mean may exceed any arbitrary percentile of the distribution (see Table 9-4). Thus, the mean of the upper five percent is by definition "conservative" both with respect to the overall mean of the distribution and to its 95th percentile, whereas the 95th percentile may not be a "conservative" estimate of the mean. In most situations, the amount of "conservatism" inherent in this new estimator will not be as extreme as it would be if a very high percentile (e.g. the 99.9th) was chosen without reference to the mean.

Thus, the issue of uncertainty subsumes the issue of conservatism in point estimates. Point estimates chosen without regard to uncertainty provide only the barest beginnings of the story in risk assessment. Excessive or insufficient conservatism can arise out of inattention to uncertainty, rather than out of a particular way of responding to uncertainty. Actions taken solely to reduce or eliminate potential conservatism will not reduce and might increase the problem of excessive reliance on point estimates.

In summary, EPA's position on the issue of uncertainty analysis (as represented in the Superfund document) seems plausible at first glance, but it might be somewhat muddled. If we know that "all risk numbers are only good to within a factor of 10," why do *any* analyses? The reason is that both the variance and the conservatism (if any) are case-specific and can rarely be estimated with adequate precision until an honest attempt at uncertainty analysis is made.

Risk Communication

Inadequate scientific and technical communication about risk is sometimes a source of error and uncertainty, and guidance to risk assessors about what to

TABLE 9-4 Calculation Showing How Mean of Upper 5% of Lognormal Distribution (M95) Relates to Other Distribution Statistics

σInx	Uncertainty factor	M_{95}	Mean	M_{95} / Mean	X_{95}	M_{95} / X_{95}	Percentile location of mean	Percentile location of M_{95}
0.25	1.3	1.75	1.03	1.7	1.51	1.16	54	98.8
0.5	1.6	2.95	1.13	2.6	2.28	1.29	60	99.2
0.75	2.1	5.03	1.32	3.8	3.43	1.46	65	98.5
1	2.7	8.57	1.65	5.2	5.18	1.65	69	98.4
1.5	4.5	27.72	3.08	9	11.79	2.35	77	98.6
1.645	5.2	38.70	3.87	10	14.97	2.59	79	98.7
1.75	5.8	49.94	4.62	10.8	17.79	2.81	81	98.7
2	7.4	94.6	7.39	12.8	26.84	3.52	84	98.8
2.5	12.2	364.16	22.76	16	61.10	5.9	89	99
3	20.1	1647.3	90.02	18.3	139.07	11.84	93.3	99.2
4	54.6	59023	2981	19.8	720.54	81.92	97.7	99.7

include in a risk analysis should include guidance about how to present it. The risk assessor must strive to be understood (as well as to be accurate and complete), just as risk managers and other users must make themselves understood when they apply concepts that are sometimes difficult. This source of uncertainty in interprofessional communication seems to be almost untouched by EPA or any other official body (AIHC, 1992).

Comparison, Ranking, And Harmonization Of Risk Assessments

As discussed in Chapter 6, EPA makes no attempt to apply a single set of methods to assess and compare default and alternative risk estimates with respect to parameter uncertainty. The same deficiency occurs in the comparison of risk estimates. When EPA ranks risks, it usually compares point estimates without considering the different uncertainties in each estimate. Even for less important regulatory decisions (when the financial and public-health impacts are deemed to be small), EPA should at least make sure that the point estimates of risk being compared are of the same type (e.g., that a 95% upper confidence bound for one risk is not compared with a median value for some other risk) and that each assessment has an informative (although perhaps sometimes brief) analysis of the uncertainty. For more important regulatory decisions, EPA should estimate the uncertainty in the *ratio* of the two risks and explicitly consider the probabilities and consequences of setting incorrect priorities. For any decisions involving risk-trading or priority-setting (e.g., for resource allocation or "offsets"), EPA should take into account information on the uncertainty in the quantities being ranked so as to ensure that such trades do not increase expected risk and that such priorities are directed at minimizing expected risk. When one or both risks are highly uncertain, EPA should also consider the probability and consequences of greatly erring in trading one risk for another, because in such cases one can lower the risk on average and yet introduce a small chance of greatly increasing risk.

Finally, EPA sometimes attempts to "harmonize" risk-assessment procedures between itself and other agencies, or among its own programs, by agreeing on a single common model assumption, even though the assumption chosen might have little more scientific plausibility than alternatives (e.g., replacing FDA's body-weight assumption and EPA's surface-area assumption with body weight to the 0.75 power). Such actions do not clarify or reduce the uncertainties in risk assessment. Rather than "harmonizing" risk assessments by picking one assumption over others when several assumptions are plausible and none of the assumptions is clearly preferable, EPA should use the preferred models for risk calculation and characterization, but present the results of the alternative models (with their associated parameter uncertainties) to further inform decision-makers and the public. However, "harmonization" does serve an important

purpose in the context of uncertainty analysis—it will help, rather than hinder, risk assessment if agencies cooperate to choose and validate a common set of *uncertainty distributions* (e.g., a standard PDF for the uncertain exponent in the "body weight to the X power" equation or a standard method for developing a PDF from a set of bioassay data).

Findings And Recommendations

The committee strongly supports the inclusion of uncertainty analysis in risk assessments despite the potential difficulties and costs involved. Even for lower-tier risk assessments, the inherent problems of uncertainty need to be made explicit through an analysis (although perhaps brief) of whatever data are available, perhaps with a statement about whether further uncertainty analysis is justified. The committee believes that a more explicit treatment of uncertainty is critical to the credibility of risk assessments and to their utility in risk management.

The committee's findings and recommendations are summarized briefly below.

Single Point Estimates and Uncertainty

EPA often reports only a single point estimate of risk as a final output. In the past, EPA has only qualitatively acknowledged the uncertainty in its estimates, generally by referring to its risk estimates as "plausible upper bounds" with a plausible lower bound implied by the boilerplate statement that "the number could be as low as zero." In light of the inability to discern how "conservative" an estimate might be unless one does an uncertainty analysis, both statements might be misleading or untrue in particular cases.

- Use of a single point estimate suppresses information about sources of error that result from choices of model, data sets, and techniques for estimating values of parameters from data. EPA should not necessarily abandon the use of single-point estimates for decision-making, but such numbers must be the product of a consideration of both the estimate of risk and its uncertainties, not appear out of nowhere from a formulaic process. In other words, EPA should be free to choose a particular point estimate of risk to summarize the risk in light of its knowledge, uncertainty, and its desire to balance errors of overestimation and underestimation; but it should first derive that number from an uncertainty analysis of the risk estimate (e.g., using a summary statistic such as the "mean of the upper 5% of the distribution"). EPA should not simply state that its generic procedures yield the desired percentile. For example (although this is an analogous procedure to deal with variability, not uncertainty), EPA's current way of

calculating the "high-end exposure estimate" (see Chapter 10) is ad hoc, rather than systematic, and should be changed.

- EPA should make uncertainties explicit and present them as accurately and fully as is feasible and needed for risk management decision-making. To the greatest extent feasible, EPA should present quantitative, as opposed to qualitative, representations of uncertainty. However, EPA should not necessarily quantify model uncertainty (via subjective weights or any other technique), but should try to quantify the parameter and other uncertainty that exists for each plausible choice of scientific model. In this way, EPA can give its default models the primacy they are due under its guidelines, while presenting useful, but distinct alternative estimates of risk and uncertainty. In the quantitative portions of their risk characterizations (which will serve as one important input to standard-setting and residual-risk decisions under the Act), EPA risk assessors should consider only the uncertainty conditional on the choice of the preferred models for dose-response relationships, exposure, uptake, etc.
- In addition, uncertainty analyses should be refined only so far as improvements in the understanding of risk and the implications for risk management justify the expenditure of the professional time and other resources that are required.

Uncertainty Guidelines

EPA committed itself in a 1992 internal memorandum (see Appendix B) to doing some kind of uncertainty analysis in the future, but the memorandum does not define when or how such analysis might be done. In addition, it does not distinguish between the different types of uncertainty or provide specific examples. Thus, it provides only the first, critical step toward uncertainty analysis.

- EPA should develop uncertainty analysis guidelines—both a general set and specific language added to its existing guidelines for each step in risk assessment (e.g., the exposure assessment guidance). The guidelines should consider in some depth all the types of uncertainty (model, parameter, etc.) in all the stages of risk assessment. The uncertainty guidelines should require that the uncertainties in models, data sets, and parameters and their relative contributions to total uncertainty in a risk assessment be reported in a written risk-assessment document.

Comparison of Risk Estimates

EPA makes no attempt to apply a consistent method to assess and compare default and alternative risk estimates with respect to parameter uncertainty. Presentations of numerical values in an incomplete form lead to inappropriate and possibly misleading comparisons among risk estimates.

- When an alternative model is plausible enough to be considered for use in risk communication, or for potentially supplanting the default model when sufficient evidence becomes available, EPA should analyze parameter uncertainty at a similar level of detail for the default and alternative models. For example, in comparing risk estimates derived from delivered-dose versus PBPK models, EPA should qualify uncertainty in the interspecies scaling factor (for the former case) and in the parameters used to optimize the PBPK equations (for the latter case). Such comparisons may reveal that given current parameter uncertainties, the risk estimate chosen would not be particularly sensitive to the judgment about which model is correct.

Harmonization of Risk Assessment Methods

EPA sometimes attempts to "harmonize" risk-assessment procedures between itself and other agencies or among its own programs by agreeing on a single common model assumption, even though the assumption chosen might have little more scientific plausibility than alternatives, (e.g., replacing FDA's body-weight assumption and EPA's surface-area assumption with body weight to the 0.75 power). Such actions do not clarify or reduce the uncertainties in risk assessment.

- Rather than "harmonizing" risk assessments by picking one assumption over others when several assumptions are plausible and none of the assumptions is clearly preferable, EPA should maintain its own default assumption for regulatory decisions but indicate that any of the methods might be accurate and present the results as an uncertainty in the risk estimate or present multiple estimates and state the uncertainty in each. However, "harmonization" does serve an important purpose in the context of uncertainty analysis—it will help, rather than hinder, risk assessment if agencies cooperate to choose and validate a common set of *uncertainty distributions* (e.g., a standard PDF for the uncertain exponent in the "body weight to the X power" equation or a standard method for developing a PDF from a set of bioassay data).

Ranking of Risk

When EPA ranks risks, it usually compares point estimates without considering the different uncertainties in each estimate.

- For any decisions involving risk-trading or priority-setting (e.g., for resource allocation or "offsets"), EPA should take into account information on uncertainty in quantities being ranked so as to ensure that such trades do not increase expected risk and such priorities are directed at minimizing expected risk. When one or both risks are highly uncertain, EPA should also consider the probability and consequences of greatly erring in trading one risk for another,

because in such cases one can lower the risk on average and yet introduce a small chance of greatly increasing risk.

Notes

1. Although variability in a risk-assessment parameter across different individuals is itself a type of uncertainty and is the subject of the following chapter, it is possible that new parameters might be incorporated into a risk assessment to model that variability (e.g., a parameter for the standard deviation of the amount of air that a random person breathes each day) and that those parameters themselves might be uncertain (see "uncertainty and variability" section in Chapter 11).

2. It is important to note that the distributions resulting from Bayesian models include various subjective judgments about models, data sets, etc. These are expressed as probability distributions but the probabilities should not be interpreted as probabilities of adverse effect but, rather, as expressions of strengths of conviction as to what models, data sets, etc. might be relevant to assessing risks of adverse effect. This is an important distinction which should be kept in mind when interpreting and using such distributions in risk management as a quantitative way of expressing uncertainty.

3. Assume that to convert from risk to the test animals to the predicted number of deaths in the human population, one must multiply by 10,000. Perhaps the laboratory dose is 10,000 times larger than the dose to humans, but 100 million humans are exposed. Thus, for example,

$$0.2\left(\frac{\text{risk}}{\text{laboratory dose}}\right)\times 10^{-4}\left(\frac{\text{laboratory dose}}{\text{ambient dose}}\right)\times 10^{8}=\left(\frac{\text{deaths}}{\text{ambient dose}}\right).$$

4. Note that characterizing risks considering only the parameter uncertainty under the preferred set of models might not be as restrictive as it appears at first glance, in that some of the model choices can be safely recast as parameter uncertainties. For example, the choice of a scaling factor between rodents and humans need not be classified as a model choice between body weight and surface area that calls for two separate "conditional PDFs," but instead can be treated as an uncertain parameter in the equation $R_{human} \propto R_{rodent}\, BW^{a}$, where a might plausibly vary between 0.5 and 1.0 (see our discussion in Chapter 11). The only constraint in this case is that the scaling model is some power function of BW, the ratio of body weights.

5. It is not always clear what percent of the distribution someone is referring to by "correct to within a factor of X." If instead of assuming that the person means with 100% confidence, we assumed that the person means 98% confidence, then the factor of X would cover two standard deviations on either side of the median, so one geometric standard deviation would be equal to X.

6. We arrive at this figure of 0.0015, or 1.5×10^{-3}, by noting that the "base case" for fenceline risk (Table 3-1 in Appendix G) is 5×10^{-4} and that "worst case estimates were two to three times higher than base case estimates."

10

Variability

Introduction And Background

It is always difficult to identify the true level of risk in an endeavor like health risk assessment, which combines measurement, modeling, and inference or educated guesswork. Uncertainty analysis, the subject of Chapter 9, enables one to come to grips with how far away from the desired answer one's best estimate of an unknown quantity might be. Before we can complete an assessment of the uncertainty in an answer, however, we must recognize that many of our questions in risk assessment have *more than one useful answer*. Variability—typically, either across space, in time, or among individuals—complicates the search for the desired value of many important risk-assessment quantities.

Chapter 11 and Appendix I-3 discuss the issue of how to aggregate uncertainties and interindividual differences in each of the components of risk assessment. This chapter describes the sources of variability[1] and appropriate ways to characterize these interindividual differences in quantities related to predicted risk.

Variability is a very well-known "fact of life" in many fields of science, but its sources, effects, and ramifications are not yet routinely appreciated in environmental health risk assessment and management. Accordingly, the first section of this chapter will step back and deal with the general phenomenon (using some examples relevant to risk assessment, but not exclusively), and then for the remainder of the chapter focus only on variability in quantities that directly influence calculations of individual and population risk.

When an important quantity is both uncertain and variable, opportunities

are created to fundamentally misunderstand or misestimate the behavior of the quantity.

To draw an analogy, the exact distance between the earth and the moon is both difficult to measure precisely (at least it was until the very recent past) and changeable, because the moon's orbit is elliptical, rather than circular. Thus, as seen in Figure 10-1, uncertainty and variability can complement or confound each other. When only scattered measurements of the earth-moon distance were available, the variation among them might have led astronomers to conclude that their measurements were faulty (i.e., ascribing to uncertainty what was actually caused by variability) or that the moon's orbit was random (i.e., not allowing for uncertainty to shed light on seemingly unexplainable differences that are in fact variable *and* predictable). The most basic flaw of all would be to simply misestimate the true distance (the third diagram in Figure 10-1) by assuming that a few observations were sufficient (after correcting for measurement error, if applicable). This is probably the pitfall that is most relevant for health risk assessment: treating a highly variable quantity as if it was invariant or only uncertain, thereby yielding an estimate that is incorrect for some of the population (or some of the time, or over some locations), or even one that is also an inaccurate estimate of the average over the entire population.

In the risk-assessment paradigm, there are many sources of variability. Certainly, the regulation of air pollutants has long recognized that chemicals differ from each other in their physical and toxic properties and that sources differ from each other in their emission rates and characteristics; such variability is built into virtually any sensible question of risk assessment or control. However, even if we focus on a single substance emanating from a single stationary source, variability pervades each stage from emission to health or ecologic end point:

- *Emissions* vary temporally, both in flux and in release characteristics, such as temperature and pressure.
- The *transport and fate* of the pollutant vary with such well-understood factors as wind speed, wind direction, and exposure to sunlight (and such less-acknowledged factors as humidity and terrain), so its concentrations around its source vary spatially and temporally.
- Individual human *exposures* vary according to individual differences in breathing rates, food consumption, and activity (e.g., time spent in each micro-environment).
- The *dose-response* relationship (the "potency") varies for a single pollutant, because each human is uniquely susceptible to carcinogenic or other stimuli (and this inherent susceptibility might well vary during the lifetime of each person, or vary with such things as other illness or exposures to other agents).

Each of these variabilities is in turn often composed of several underlying variable phenomena. For example, the natural variability in human weight is due to the interaction of genetic, nutritional, and other environmental factors.

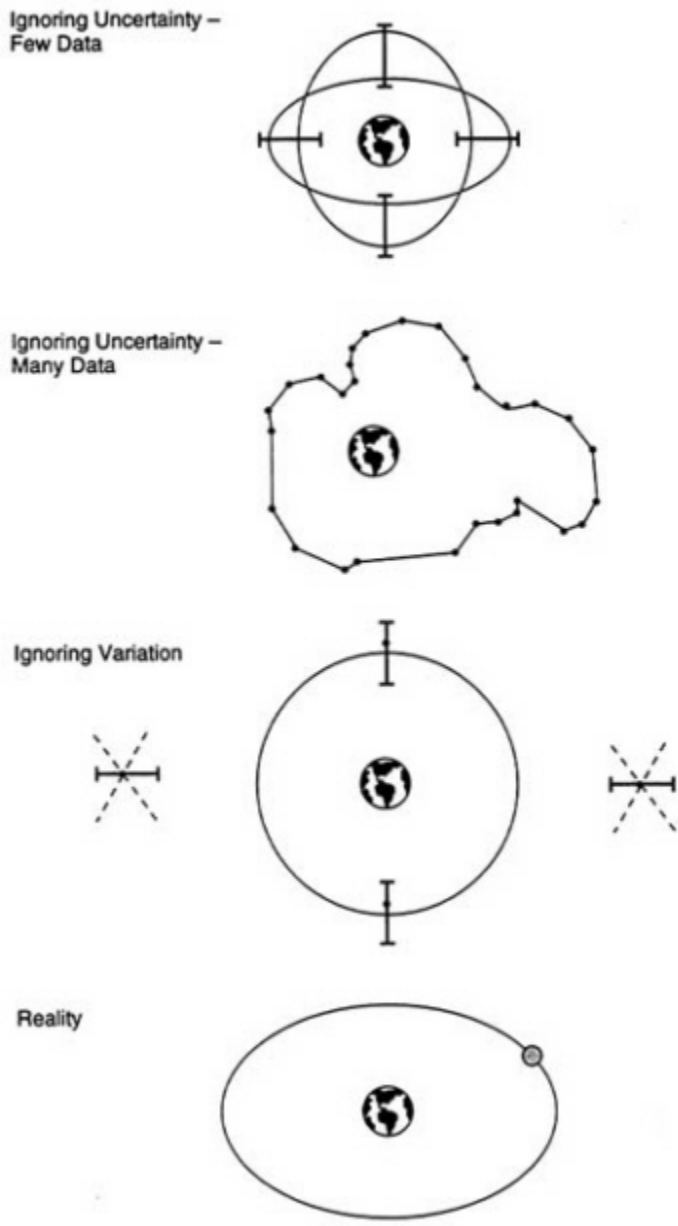


FIGURE 10-1 Effects of ignoring uncertainty versus ignoring variability in measuring the distance between the earth and the moon.

According to the central limit theorem, variability that arises from independent factors that act multiplicatively will generally lead to an approximately lognormal distribution across the population or spatial/temporal dimension (as is commonly observed when concentrations of air pollutants are plotted).

When there is more than one desired answer to a scientific question where the search for truth is the end in itself, only two responses are ultimately satisfactory: gather more data or rephrase the question. For example, the question "How far away is the moon from the earth?" cannot be answered both simply and correctly. Either enough data must be obtained to give an answer of the form "The distance ranges between 221,460 and 252,710 miles" or "The moon's orbit is approximately elliptical, with a minor axis of 442,920 miles, a major axis of 505,420 miles, and an eccentricity of 0.482," or the question must be reduced to one with a single right answer (e.g., "How far away is the moon from the earth *at its perigee?*").

When the question is not purely scientific, but is intended to support a social decision, the decision-maker has a few more options, although each course of action will have repercussions that might foreclose other courses. Briefly, variability in the substance of a regulatory or science-policy question can be dealt with in four basic ways:

1. *Ignore the variability and hope for the best*. This strategy tends to be most successful when the variability is small and any estimate that ignores it will not be far from the truth. For example, the Environmental Protection Agency's (EPA's) practice of assuming that all adults weight 70 kg is likely to be correct to within ±25% for most adults and probably valid to within a factor of 3 for virtually all adults. However, this approach may not be appropriate for children, where variability may be large (NRC, 1993e).
2. *Explicitly disaggregate the variability*. Where the quantity seems to change smoothly and predictably over some range, continuous mathematical models may be fitted to the data in place of a discrete step function. An example might be the fitting of sine waves to annual concentration cycles for a particular pollutant. In other cases, it is easier to disaggregate the data by considering all or the relevant subgroups or subpopulations. For interindividual variability, this involves dividing the population into as many subpopulations as deemed necessary. For example, one might perform a separate risk assessment for short-term exposure to high levels of ionizing radiation for each 10-year age interval in the population, to take account of age-related differences in susceptibility. For temporal variability, it involves modeling or measuring in a discrete, rather than a continuous, fashion, on an appropriate time scale. For example, a specific type of air-pollution monitor might collect air for 15 min of each hour and report the 15-min average concentration of some pollutant. Such values might then be further aggregated to produce summary values at an even coarser time scale. For spatial variability, it involves choosing an appropriate subregion, e.g., modeling

the extent of global warming or cooling for each 10-deg swath of latitude around the globe, rather than predicting a single value for the entire planet, which might mask substantial and important regional differences. In each case, the common thread appears: when variability is "large" over the entire data set, the variability within each subset can become sufficiently "small" ("small" in the sense of the body-weight example in the paragraph above), if the data are disaggregated into an appropriate number of qualitatively distinct subsets. The strategy tends to be most successful when the stakes are so high (or the data or estimates so easy to obtain) that the proliferation of separate assessments does not consume inordinate amounts of resources. In contrast, in studies of a phenomenon such as global climate change, where the stakes are quite high, the estimates may also be quite hard to obtain on a highly disaggregated basis.

3. In health risk assessment, the choice of the averaging time used to transform the variable quantity into a more manageable form is crucially important. In general, for the assessment of acute toxicity, estimates of the variability in exposure and/or uptake over relatively short periods (minutes, hours, days) are needed. For chronic effects such as cancer, one might model exposure and/or update over months or years without losing needed information, since short-term "peaks and valleys" would matter for cancer risk assessment only insofar as they affected the long-term or lifetime average exposure.[2] The longer-term variability will generally, though not always, be significantly less marked than the variation over the short-term (but see Note 3). Moreover, the shorter the averaging time, the more such periods will be contained in an individual's lifetime, and the more opportunity there will be for rare fluctuations in exposure or uptake to produce significant risks. This, for example, explains why regulators concerned with the health effects of tropospheric ozone consider the combination of peak short-term concentration *and* peak activity (e.g., the "exercising asthmatic"). In all cases, the exposure assessor needs to determine which time periods are relevant for which toxic effects, and then see whether available data measuring exposure, uptake, internal dose rates, etc., can provide estimates of both the average and the variability over the necessary averaging time.

3. *Use the average value of a quantity that varies*. This strategy is not the same as ignoring the variability; ideally, it follows from a decision that the average value can be *estimated reliably in light of the variability*, and that it is a good surrogate for the variable quantity. For example, EPA often uses 70 kg as the average body weight of an adult, presumably because although many adults weigh as little as 40 kg and as much as 100 kg, the average weight is almost as useful as (and less complicated than) three different "scenario" values or an entire distribution of weights. In the same vein, a layperson might be content in knowing the average value of the moon's distance from the earth, rather than the minimum, average, and maximum (let alone a complete mathematical description of its orbit)—whereas the average alone would be useless, or even dangerous, to the National Aeronautics and Space Administration in

planning an Apollo mission. Thus, this strategy tends to be most successful (and indeed might be the only sensible strategy) when the variability is small[3] or when the quantity is itself an input for a model or decision in which the average value of the end result (the combination of several quantities) is all that matters, either for scientific or policy reasons. An example of a scientific rationale for using the average value is the long-term average concentration of a carcinogen in air. If the dose-response function is linear (i.e., "potency" is a single number), the end result (risk) is proportional to the average concentration. If the concentration is, say, 10 ppm higher than the average in one week and 10 ppm lower than the average in another week, this variability will have no effect on an exposed person's lifetime risk, so it is biologically unimportant. An example of a policy rationale is the use of the expected number of cancer cases in a population exposed to varying concentrations of an airborne carcinogen. If it is determined for a particular policy rationale that the distribution of individual risks across the population does not matter, then the product of *average* concentration, potency and population size equals the expected incidence, and the spread of concentrations about the average concentration is similarly unimportant. The average value is also the summary statistic of choice for social decisions when there is an opportunity for errors of underestimation and overestimation (which lead to underregulation and overregulation) to even out over a large set of similar choices over the long run.

There are at least two reasons why large variabilities can lead to precarious decisions if the average value is used. The obvious problem is that individual characteristics of persons or situations far from the average are "averaged away" and can no longer be identified or reported. A less obvious pitfall occurs when the variability is dichotomous (or has several discrete values) and the average corresponds to a value that does not exist in nature. If men and women respond markedly differently to some exposure situation, for example, the decision that would be appropriate if there existed an "average person" (midway between man and woman) might be inappropriate for either category of real person (see Finkel, 1991).

4. *Use a maximum or minimum of a quantity that varies*. This is perhaps the most common way of dealing with variability in risk assessment—to focus attention on one period (e.g., the period of peak exposure), one spatial subregion (e.g., the location where the "maximally exposed individual" resides), or one subpopulation (e.g., exercising asthmatics or children who ingest pathologically large amounts of soil) and ignore the rest. This strategy tends to be most successful when the measures needed to protect or account for the person (or situation) with the extreme value will *also* suffice for the remainder of the distribution. It is also important to ensure that this strategy will not impose inordinate costs, compared with other approaches (such as using different controls for each subregion or population or simply controlling less stringently by using the average value instead of the extreme "tail").

The crucial point to bear in mind about all four of those strategies for dealing with variability is that unless someone measures, estimates, or at least roughly models the extent and nature of the variability, any strategy will be precarious. It stands to reason that strategy 1 ("hope for the best") hinges on the assumption that the variability is small—an assumption whose verification requires at least some attention to variability. Similarly, strategy 2 requires the definition of subregions or subpopulations in each of which the variability is small, so care must be taken to avoid the same conundrum that applies to strategy 1. (It is difficult to be sure that you can ignore variability until you think about the possible consequences of ignoring it.) Less obviously, one still needs to be somewhat confident that one has a handle on the variability in order to reduce the distribution to either an average (strategy 3) or a "tail" value (strategy 4). We *know* that 70 kg is an average adult body weight (and that virtually no adults are above or below 70 kg by more than a factor of 3), because weight is directly observable *and* because we know the mechanism by which people grow and the biologic limits of either extreme. Armed with our senses and this knowledge, we might need only a few observations to pin down roughly the minimum, the average, and the maximum. But what about a variable like "the rate at which human liver cells metabolize ethylene dibromide into its glutathione conjugate"? *Here a few direct measurements or a few extrapolations from animals may not be adequate,* because in the absence of any firm notion of the spread of this distribution within the human population (or the mechanisms by which the spread occurs), we cannot know how reliably our estimate of the average value reflects the true average, nor how well the observed minimum and maximum mirror the *true* extremes.

The distribution for an important variable such as metabolic rate should thus explicitly be considered in the risk assessment, and the reliability of the overall risk estimate should reflect knowledge about both the uncertainty and the variability in this characteristic. The importance of a more accurate risk estimate may motivate additional measurements of this variable, so that its distributions may be better defined with these additional data.

This chapter concentrates on how EPA treats variability in emissions, exposures, and dose-response relationships, to identify which of the four strategies it typically uses and to assess how adequately it has considered each choice and its consequences. The goals of this chapter are three: (1) to indicate how EPA can increase its sophistication in defining variability and handling its effects; (2) to provide information as to how to improve risk *communication,* so that Congress and the public understand at least which variabilities are and which are not accounted for, and how EPA's handling of variability affects the "conservatism" (or lack thereof) inherent in its risk numbers; and (3) to recommend specific research whose results could lead to useful changes in risk-assessment procedures.

In recent years, EPA has begun to increase its attention to variability. Moreover,

the lack of attention in the past was due in part to a set of choices to erect a set of conservative default options (strategy 4 above) instead of dealing with variability explicitly. In theory at least, the question "How do you determine the extreme of a distribution without knowing the whole distribution?" can be answered by setting a highly conservative default and placing the burden of proof on those who wish to relax the default by showing that the extreme is unrealistic even as a "worst case." For example, the concept of the MEI (someone who breathes pollutants from the source for 70 years, 24 hours per day, at a specified location near a plant boundary) has been criticized as unrealistic, but most agree that as a summary of the population distribution of "number of hours spent at a given location during a lifetime" it might be a reasonable place to start from as a conservative short-cut for the entire distribution.

EPA has also tackled interindividual variability squarely in *Exposure Factors Handbook* (EPA, 1989c), which provides various percentiles (e.g., 5^{th}, 25^{th}, 50^{th}, 75^{th}, 95^{th}) of the observed variability distributions for some components of exposure assessment, such as breathing rates, water ingestion, and consumption of particular foodstuffs. This document has not yet become a standard reference for many of EPA's offices, however. In addition, as we will discuss below, EPA has not dealt adequately with several other major sources of variability. *As a result, EPA's methods to manage variability in risk assessment rely on an ill-characterized mix of some questionable distributions, some verified and unverified point values intended to be "averages," some verified and unverified point values intended to be "worst cases," and some "missing defaults," that is, hidden assumptions that ignore important sources of variability*.

Moreover, several trends in risk assessment and risk management are now increasing the urgency of a broad and well-considered strategy to deal with variability. The three most important of these trends are the following:

- *The emergence of more sophisticated biological models for risk assessment*. As pharmacokinetic models replace the administered assumption and as cell-kinetics models (such as the Moolgavkar-Venzon-Knudson model) replace the linearized-multistage model, default models that ignored human variability or took conservative measures to sidestep it will be supplanted by models that explicitly contain values of biologic measures intended to represent the human population. If the latter models ignore variability or use unverified surrogates for presumed average or worst-case properties, risk assessment might take a step backwards, becoming either less or more conservative without anyone's knowledge.
- *The growing interest in detailed assessments of the actual exposures that people face, rather than hypothetical worst-case exposures*. To be trustworthy, both average and worst-case surrogates for variability require some knowledge of the rest of the distribution, as mentioned above. However, it is not well recognized that the average might be *more* sensitive to the extreme portions of

the whole distribution than an upper percentile might be, such as the 95th. In addition, the use of such terms as *actual* and *best estimates* carries an expectation of precision that might apply to only *part* of the exposure assessment, dose-response relationship, or risk assessment. If, for example, we could precisely measure the airborne concentration of a pollutant in a community around a stationary source (i.e., understand the spatial variability), but did not know the population distribution of breathing rates, we could not predict *anyone's* "actual exposure." In fact, even if we knew *both* distributions but could not superimpose them (i.e., know which breathing rates went with which concentrations), the predictions would be as variable as either of the underlying distributions. These circumstances speak to the need for progress in many kinds of research and data collection at once, if we wish to improve the power and the realism of risk assessment.

- *The growing interest in risk-reduction measures that target people, rather than sources*. It should go without saying that if government or industry wishes to eliminate unacceptably high risks to particular persons by purchasing their homes, providing them with bottled water, restricting access to "hot spots" of risk, etc., it needs to know precisely who those persons are and where or when those hot spots are occurring. Even if such policies were not highly controversial and difficult to implement in an equitable and socially responsive way, merely identifying the prospective targets of such policies may well presuppose a command of variability beyond our current capabilities.

Exposure Variability

Variability in human response to pollutants emitted from a particular source or set of sources can arise from differences in characteristics of exposure, uptake, and personal dose-response relationships (susceptibility). Exposure variability in turn depends on variability in all the factors that affect exposure, including emissions, atmospheric processes (transport and transformation), personal activity, and the pollutant concentration in the microenvironments where the exposures occur. Information on those variabilities is not routinely included in EPA's exposure assessments, probably because it has been difficult to specify the distributions that describe the variations.

Human exposure results from the contact of a person with a substance at some nonzero concentration. Thus, it is tied to personal activities that determine a person's location (e.g., outdoors vs. indoors, standing downwind of an industrial facility vs. riding in a car, in the kitchen vs. on a porch); the person's level of activity and breathing rate influences the uptake of airborne pollutants. Exposure is also tied to emission rates and atmospheric processes that affect pollutant concentrations in the microenvironment where the person is exposed. Such processes include infiltration of outside air indoors, atmospheric advection (i.e., transport by the prevailing wind), diffusion (i.e., transport by atmospheric turbulence,

chemical and physical transformation, deposition, and re-entrainment—variability in each process tends to increase the overall variability in exposure. The variabilities in emissions atmospheric processes, characteristics of the microenvironment, and personal activity are not necessarily independent of each other; for example, personal activities and pollutant concentrations at a specific location might change in response to outdoor temperature; they might also differ between weekends and weekdays because the level of industrial activity changes.

Emissions Variability

There are basically four categories of emission variability that may need separate assessment methods, depending on the circumstances:

- Routine—this is the type most frequently covered by current approaches.
- Ordinary maintenance—special emissions may occur, for example, when the bag house is cleaned. In other cases certain emissions may only occur during maintenance, as when a specific volatile cleaner is routinely used to scour or wash out a reaction tank. These can be deliberately observed and monitored to obtain needed emissions information, if this mode is deemed likely to be significant.
- Upsets and breakdowns—unusual operating conditions that may recur within average periods of days, weeks, or months, depending on the facility/process. A combination of observations and modeling approaches may be needed here.
- Catastrophic failures—large explosions, ruptures of storage tanks, etc.

The last category is addressed in a separate section of the Clean Air Act and is not discussed in this report.

At least two major factors influence variability in emissions as it affects exposure assessment. First, a given source typically does not emit at a constant rate. It is subject to such things as load changes, upsets, fuel changes, process modifications, and environmental influences. Some sources are, by their nature, intermittent or cyclical. A second factor is that two similar sources (e.g., facilities in the same source category) can emit at different rates because of differences in such things as age, maintenance, or production details.

The automobile is an excellent example of both causes. Consider a single, well-characterized car with an effective control system. When it is started, the catalyst has not warmed up, and emissions can be high. Almost half the total automobile emissions in, say, Los Angeles can occur during the cold-start period. After the catalyst reaches its appropriate temperature range, it is extremely effective (>90%) at removing organic substances, such as benzene and formaldehyde, during most of the driving period. However, hard accelerations can overwhelm the system's capabilities and lead to high emissions. Those variations can lead to spatial and temporal distributions of emissions in a city (e.g.,

high emissions in areas with a large number of cold starts, particularly in the morning). The composition of the emissions, including the toxic content, differs between cold-start and driving periods. Emissions also differ between cars—often dramatically. Because of differences in control equipment, total emissions can vary, and emissions between cycles can vary between cars (e.g., cold-start vs. evaporative emissions). A final notable contribution to emission variability in automobiles is the presence of super-emitters, whose control systems have failed and may emit organic substances at a rate 10 times that of a comparable vehicle that is operating properly.

Thus, an exposure analysis based on source-category average emissions will miss the variability in sources within that category. And, exposure analyses that do not account for temporal changes in emissions from a particular source will miss an important factor, especially to the extent that emissions are linked to meteorologic conditions. In many cases, it is difficult or impossible to know a priori how emissions will vary, particularly because of upsets in processes that could lead to high exposures over short periods.

Atmospheric Process Variability

Meteorologic conditions greatly influence the dispersion, transformation, and deposition of pollutants. For example, ozone concentrations are highest during summer afternoons, whereas carbon monoxide and benzene concentrations peak in the morning (because of the combination of large emissions and little dilution) and during the winter. Formaldehyde can peak in the afternoon during the summer (because of photochemical production) and in the morning in the winter (because of rush-hour emissions and little dilution). Concentrations of primary (i.e., emitted) pollutants, such as benzene and carbon monoxide, are higher in the winter in urban areas, whereas those of many secondary pollutants (i.e., those resulting from atmospheric transformations of primary pollutants), such as ozone, are higher in the summer. Meteorologic conditions may also play a role in regional variations. Some areas experience long periods of stagnant air, which lead to very high concentrations of both primary and secondary pollutants. An extreme example is the London smog that led to high death rates before the mid-1950s. Wind velocity and mixing height also influence pollutant concentrations. (Mixing height is the height to which pollutants are rapidly mixed due to atmospheric turbulence; in effect, it is one dimension of the atmospheric volume in which pollutants are diluted.) They are usually correlated; the prevailing winds and velocities in the winter, when the mixing height is low, can be very different from those in the summer.

Some quantitative information is available about the impact of meteorologic variability on pollutant concentrations. Concentrations measured at one location over some period tend to follow a lognormal distribution. There are significant fluctuations in the concentrations about the medians (e.g., Seinfeld, 1986), which

often vary by a factor of more than 10. The extreme concentrations are usually related to time and season. The relative magnitudes and frequencies of such fluctuations in concentration increase as distance from the source decreases. Pollutant transport over complex terrain (e.g., presence of hills or tall buildings), which is generally difficult to model, can further increase relative differences in extreme concentrations about the medians. Two examples of the influence of complex terrain are Donora, Pennsylvania (in a river valley), and the Meuse Valley in Belgium. In those areas, as in London, periods of extremely high pollutant concentrations led to a period of increased deaths. Estimates of concentration over flat terrain cannot capture such effects.

Empirical data on concentration variability are sparse, except for a few pollutants, notably the criteria pollutants (including carbon monoxide, ozone, sulfur dioxide, and particulate matter). Some information on variations in formaldehyde and benzene concentrations is also available. One interesting study that considered air-pollutant exposure during commuting in the Los Angeles area was conducted by the South Coast Air Quality Management District (SCAQMD, 1989). The authors looked at exposure dependence on seasonal, vehicular-age, and freeway-use variations. They found that drivers of older vehicles had greater exposure to benzene and that exposure to benzene, formaldehyde, ethylene, and chromium was greater in the winter, although exposure to ethylene dichloride was greater in the summer. They did not report the variability in exposure between similar vehicles or distributions of the exposures (e.g., probability density functions).

Microenvironmental and Personal-Activity Variability

Microenvironmental variability, particularly when compounded with differences in personal activity, can contribute to substantial variability in individual exposure. For example, the lifetime-exposed 70-year-old has been faulted as an extreme case, but it is instructive to consider this hypothetical person in the distribution of personal activity traits. Although it is unlikely, this 70-year lifetime exposure activity pattern is one end of the spectrum in the variability of personal activity and time spent in a specific microenvironment.

Concentrations in various microenvironments vary considerably and depend on a variety of factors, such as species, building type, ventilation system, locality of other sources, and street canyon width and depth. Both the Los Angeles study (SCAQMD, 1989) and a New Jersey study (Weisel et al., 1992) revealed that exposure can be increased during commuting, particularly if the automobile itself is defective. The primary sources of many air pollutants are indoors, so their highest concentrations are found there. Those concentrations can be 10-1,000 times the outdoor concentrations (or even greater). However, the difference between outdoor and indoor concentrations of pollutants is not nearly so great when the indoor location is ventilated. Concentrations of compounds that do not

react rapidly with or settle on surfaces, such as carbon monoxide and many organic compounds might not decrease significantly when ventilated indoors. If there are additional sources of these compounds indoors, their concentrations might, in fact, increase. Concentrations of more reactive compounds, such as ozone, can decrease by a factor of 2 or more, depending on ventilation rate and the ventilation system used (Nazaroff and Cass, 1986). Particles can also be advected indoors (Nazaroff et al., 1990). One concern is that the ventilation of outdoor pollutants indoors can increase the formation of other pollutants (Nazaroff and Cass, 1986; Weschler et al., 1992). The lifetime-exposed person sitting on the porch outside his home may be at one extreme for exposure to emissions from an outdoor stationary source, but may be at the other extreme for net air-pollutant exposure; such a person may have effectively avoided "hot" microenvironments in both the home and the automobile.

Increased personal activity leads to a larger uptake, and this will add to variability by as much as a factor of about 2 or more. The activity-related component of variability depends on both the microenvironmental variability (e.g., outdoors vs. indoors) and personal characteristics (e.g., children vs. adults).

Variability In Human Susceptibility

Person-to-person differences in behavior, genetic makeup, and life history together confer on individual people unique susceptibilities to carcinogenesis (Harris, 1991). Such interindividual differences can be inherited or acquired. For example, inherited differences in susceptibility to physical or chemical carcinogens have been observed, including a substantially increased risk of sunlight-induced skin cancer in people with xeroderma pigmentosum, of bladder cancer in dyestuff workers whose genetic makeup results in the "poor acetylator" phenotype, and of bronchogenic carcinoma in tobacco smokers who have an "extensive debrisoquine hydroxylator" phenotype (both are described further in Appendix H). Similarly among different inbred and outbred strains of laboratory animals (and within particular outbred strains) exposed to carcinogenic initiators or tumor promoters there may be a factor of 40 variation in tumor response (Boutwell, 1964; Drinkwater and Bennett, 1991; Walker et al., 1992). Acquired differences that can significantly affect an individual's susceptibility to carcinogenesis include the presence of concurrent viral or other infectious diseases, nutritional factors such as alcohol and fiber intake, and temporal factors such as stress and aging.

Appendix H describes three classes of factors that can affect susceptibility: (1) those which are rare in the human population but which confer very large increases in susceptibility upon those affected; (2) those which are very common but only marginally increase susceptibility; and (3) those which may be neither rare nor of marginal importance to those affected. The Appendix provides particular detail on five of the determinants that fall into this third group. This

material in Appendix H represents both a compilation of existing literature as well as some new syntheses of recent studies; we commend the reader's attention to this important information.

Overall Susceptibility

Taken together, the evidence regarding the individual mediators of susceptibility described in Appendix H supports the plausibility of a continuous distribution of susceptibility in the human population. Some of the individual determinants of susceptibility, such as concentrations of activating enzymes or of proteins that might become oncogenic, may themselves exist in continuous gradations across the human population. Even factors that have long been thought to be dichotomous are now being revealed as more complicated—e.g., the recent finding that a substantial fraction of the population is heterozygous for ataxia-telangiectasia and has a susceptibility midway between that of ataxia-telangiectasia homozygotes and that of "normal" people (Swift et al., 1991). Most important, the combination of a large number of genetic, environmental, and lifestyle influences, even if each were bimodally distributed, would likely generate an essentially continuous overall susceptibility distribution. As Reif (1981) has noted, "we would expect to find in [the outbred human population] what would be the equivalent result of outbreeding different strains of inbred mice: a spectrum of different genetic predispositions for any particular type of tumor."

A working definition of the breadth of the distribution of "interindividual variability in overall susceptibility to carcinogenesis" is as follows: If we identified persons of high susceptibility (say, we knew them to represent the 99^{th} percentile of the population distribution) and low susceptibility (say, the 1^{st} percentile), we could estimate the risks that each would face if subjected to the same exposure to a carcinogen. If the estimated risk to the first type of person were 10^{-2} and the estimated risk to the second type of person were 10^{-6}, we could say that "human susceptibility to this chemical varies by at least a factor of 10,000."[4]

There are two distinct but complementary approaches to estimating the form and breadth of the distribution of interindividual variability in overall susceptibility to carcinogenesis. The biologic approach is a "bottom-up" method that uses empirical data on the distribution of particular factors that mediate susceptibility to model the overall distribution. In the major quantitative biologic analysis of the possible extent of human variations in susceptibility to carcinogenesis, Hattis et al. (1986) reviewed 61 studies that contained individual human data on six characteristics that are probably involved causally in the carcinogenic process. The six were the half-life of particular biologically active substances in blood, metabolic activation of drugs (in vivo) and putative carcinogens (in vitro), enzymatic detoxification, DNA-adduct formation, the rate of DNA repair (as measured by the rate of unscheduled DNA synthesis induced by UV light), and

the induction of sister-chromatid exchanges after exposure of lymphocytes to x-rays. They estimated the overall variability in each factor by fitting a lognormal distribution to the data and then propagated the variabilities by using Monte Carlo simulation and assuming that the factors interacted multiplicatively and were statistically independent. Their major conclusion was that the logarithmic standard deviation of the susceptibility distribution lies between 0.9 and 2.7 (90% confidence interval). That is, the difference in susceptibility between the most sensitive 1% of the population and the least sensitive 1% might be as small as a factor of 36 (if the logarithmic standard deviation was 0.9) or as large as a factor of 50,000 (if the logarithmic standard deviation was 2.7).[5]

The alternative approach is inferential or "top-down," and combines epidemiologic data with a demographic technique known as heterogeneity dynamics. Heterogeneity dynamics is an analytic method for describing the changing characteristics of a heterogeneous population as its members age. The power of the heterogeneity-dynamics approach to explain initially puzzling aspects of demographic data, as well as to challenge simplistic explanations of population behavior, stems from its emphasis on the divergence between forces that affect individuals and forces that affect populations (Vaupel and Yashin, 1983). The most fundamental concept of heterogeneity dynamics is that individuals change at rates different from those of the cohorts they belong to, because the passage of time affects the composition of the cohort as it affects the life prospects of each member. In a markedly heterogeneous population, the overall death rate can decline with age, even though every individual faces an ever-increasing risk of death, simply because the population as a whole grows increasingly more "resistant" to death as the more susceptible members are preferentially removed. Specifically with regard to cancer, heterogeneity dynamics can examine the progressive divergence of observed human age-incidence functions (for many tumor types) away from the function that is believed to apply to an individual's risk as a function of age—namely, the power function of age formalized in the 1950s by Armitage and Doll (which posits that risk increases proportionally with age raised to an integral exponent, probably 4, 5, or 6). In contrast with groups of inbred laboratory animals, which do exhibit age-incidence functions that generally obey the Armitage-Doll model, in humans the age-incidence curves for many tumor types begin to level off and plateau at higher ages.

Many of the pioneering studies that used heterogeneity dynamics to infer the amount of variation in human susceptibility to cancer used cross-sectional data, which might have been confounded by secular changes in exposures to carcinogenic stimuli (Sutherland and Bailar, 1984; Manton et al., 1986). One investigation that built on the previous body of work was that of Finkel (1987), who assembled longitudinal data on cancer mortality, including the age at death and cause of death of all males and females born in 1890, for both the United States and Norway. That study separately examined deaths due to lung cancer and colorectal cancer and tried to infer the amount of population heterogeneity that

could have caused the observed age-mortality relationships to diverge from the Armitage-Doll (age^N) function that should apply to the population if all humans are of equal sensitivity. The study concluded that as a first approximation, the amount of variability (for either sex, either disease, and either country) could be roughly modeled by a lognormal distribution with a logarithmic standard deviation on the order of 2.0 (i.e., general agreement with the results of Hattis et al., 1986). That is, about 5% of the population might be about 25 times more susceptible than the average person (and a corresponding 5% about 25 times less susceptible); about 2.5% might be 50 times more (or less) susceptible than the average, and about 1% might be at least 100 times more (or less) susceptible.

A later analysis (Finkel, in press) showed that such a conclusion, if borne out, would have important implications not only for assessing risks to individuals, but for estimating population risk in practice. In a highly heterogeneous population, quantitative uncertainties about epidemiological inferences drawn from relatively small subpopulations (thousands or fewer), as well as the frequent application of animal-based risk estimates to similarly "small" subpopulations, will be increased by the possibility that the *average* susceptibility of small groups varies significantly from group to group.

The issue of susceptibility is an important one for acute toxicants as well as carcinogens. The NRC Committee on Evaluation of the Safety of Fishery Products addressed this issue in depth in their report entitled *Seafood Safety* (NRC, 1991b). Guidelines for the assessment of acute toxic effects in humans have recently been published by the NRC Committee on Toxicology (NRC, 1993d).

Conclusions

This section records the results of the committee's analysis of EPA's practice on variability.

Exposure Variability and the Maximally Exposed Individual

One of the contentious defaults that has been used in past air-pollutant exposure and risk assessments has been the maximally exposed individual (MEI), who was assumed to be the person at greatest risk and whose risk was calculated by assuming that the person resided outdoors at the plant boundary, continuously for 70 years. This is a worst-case scenario (for exposure to the particular source only) and does not account for a number of obvious factors (e.g., the person spends time indoors, going to work, etc.) and other likely events (e.g., changing residence) that would decrease exposure to the emissions from the specific source. This default also does not account for other, possibly countervailing factors involved in exposure variability discussed above. Suggestions to remedy this shortcoming have included decreasing the point estimate for residence time

at the location to account for population mobility, and use of personal-activity models (see Chapters 3 and 6).

EPA's most recent exposure-assessment guidelines (EPA, 1992a) no longer use the MEI, instead coining the terms "high-end exposure estimates" (HEEE) and "theoretical upper-bounding exposure" (TUBE) (see Chapter 3). According to the new exposure guidelines (Section 5.3.5.1), a high-end risk "means risks above the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest risk." The EPA Science Advisory Board had recommended that exposures or risks above the 99.9th percentile be regarded as "bounding estimates" (i.e., use of the 99.9th percentile as the HEEE) for large populations (assuming that unbounded distributions such as the lognormal are used as inputs for calculating the exposure or risk distribution). For smaller populations, the guidelines state that the choice of percentile should be based on the objective of the analysis. However, neither the HEEE nor the TUBE is explicitly related to the expected MEI.

The new exposure guidelines (Section 5.3.5.1) suggest four methods for arriving at an estimator of the HEEE. These are, in descending order of sophistication:

- "If sufficient data on the distribution of doses are available, take the value directly from the percentile(s) of interest within the high end;"
- "if … data on the parameters used to calculate the dose are available, a simulation (such as an exposure model or Monte Carlo simulation) can sometimes be made of the distribution. In this case, the assessor may take the estimate from the simulated distribution;"
- "if some information on the distribution of the variables making up the exposure or dose equation … is available, the assessor may estimate a value which falls into the high end … The assessor often constructs such an estimate by using maximum or near-maximum values for one or more of the most sensitive variables, leaving others at their mean values;"
- "if almost no data are available, [the assessor can] start with a bounding estimate and back off the limits used until the combination of parameter values is, in the judgment of the assessor, clearly in the distribution of exposure or dose … The availability of pertinent data will determine how easily and defensibly the high-end estimate can be developed by simply adjusting or backing off from the ultraconservative assumptions used in the bounding estimates."

The first two methods are much preferable to the last two and should be used whenever possible. Indeed, EPA should place a priority on collecting enough data (either case-specific or generic) that the latter two methods will not be needed in estimating variability in exposure. The distribution of exposures, developed from measurements or modeling results or both, should be used to estimate population exposure, as an input in calculating population risk. It can also be used to estimate the exposure of the maximally exposed person. For

example, the most likely value of the exposure to the most exposed person is generally the 100[(N-1)/N]th percentile of the cumulative probability distribution characterizing interindividual variability in exposures, where N is the number of persons used to construct the exposure distribution. This is a particularly convenient estimator to use because it is independent of the shape of the exposure distribution (see Appendix I-3). Other estimators of exposure to the highest, or jth highest for some *j*<;N, person exposed are available (see Appendix I-3). The committee recommends that EPA explicitly and consistently use an estimator such as 100[(N-1)/N], because it, and not a vague estimate "somewhere above the 90th percentile," is responsive to the language in CAAA-90 calling for the calculation of risk to "the individual most exposed to emissions. …"

In recent times, EPA has begun incorporating into distributions of exposure assumptions that are based on a national average of years of residence in a home, as a replacement for its 70-year exposure assumption (e.g., an average lifetime). Proposals have been made for a similar "departure from default" for the time an individual spends at a residence each day, as a replacement for the 24 hours assumption. However, such analyses make the assumption that individuals move to a location of zero exposure when they change residences during their lifetime or leave the home each day. But, people moving from one place to another, whether it be changing the location of their residence or moving from the home to office, can vary greatly in their exposure to any one pollutant, from relatively high exposures to none. Furthermore, some exposures to different pollutants may be considered as interchangeable: moving from one place to another may yield exposures to different pollutants which, being interchangeable in their effects, can be taken as an aggregate, single "exposure." This assumption of interchangeability may or may not be realistic; however, because people moving from place to place can be seen as being exposed over time to a mixture of pollutants, some of them simultaneously and others at separate times, a simplistic analysis of residence times is not appropriate. The real problem is, in effect, a more complex problem of how to aggregate exposure to mixtures as well as one of multiple exposures of varying level of intensities to a single pollutant.

Thus, a simple distribution of residence times may not adequately account for the risks of movement from one region to another, especially for persons in hazardous occupations, such as agricultural workers exposed to pesticides, or persons of low socioeconomic status who change residences. Further, some subpopulations that might be more likely to reside in a high-exposure region might also be less mobile (e.g., owing to socioeconomic conditions). For these reasons, the default residency assumption for the calculation of the maximally exposed individual should remain at the mean of the current U.S. life expectancy, in the absence of supporting evidence otherwise. Such evidence could include population surveys of the affected area that demonstrate mobility outside regions of residence with similar exposures to similar pollutants. Personal activity (e.g., daily and seasonal activities) should be included.

If in a given case EPA determines that it must use the third method (combining various different "maximum," "near-maximum," and average values for inputs to the exposure equation) to arrive at the HEEE, the committee offers another caution: EPA has not demonstrated that these combinations of point estimates do in fact yield an output that reliably falls at the desired location within the overall distribution of exposure variability (that is, in the "conservative" portion of the distribution, but not above the confines of the entire distribution). Accordingly, EPA should validate (through generic simulation analyses and specific monitoring efforts) that its point-estimation methods do reasonably and reliably approximate what would be achieved via the more sophisticated direct-measurement or Monte Carlo methods (that is, a point estimate at approximately the 100[(N-1)/N] percentile of the distribution). The fourth method, it should go without saying, is highly arbitrary and should not be used unless the bounding estimate can be shown to be "ultraconservative" and the concept of "backing off" is better defined by EPA.

Susceptibility

Human beings vary substantially in their inherent susceptibility to carcinogenesis, both in general and in response to any specific stimulus or biologic mechanism. No point estimate of the carcinogenic potency of a substance will apply to all individuals in the human population. Variability affects each step in the carcinogenesis process (e.g., carcinogen uptake and metabolism, DNA damage, DNA repair and misrepair, cell proliferation, tumor progression, and metastasis). Moreover, the variability arises from many independent risk factors, some inborn and some environmental. On the basis of substantial theory and some observational evidence, it appears that some of the individual determinants of susceptibility are distributed bimodally (or perhaps trimodally) in the human population; in such cases, a class of hypersusceptible people (e.g., those with germ-line mutations in tumor-suppressor genes) might be at tens, hundreds, or thousands of times greater risk than the rest of the population. Other determinants seem to be distributed more or less continuously and unimodally, with either narrow or broad variances (e.g., the kinetics or activities of enzymes that activate or detoxify particular pollutants).

To the extent that those issues have been considered at all with respect to carcinogenesis, EPA and the research community have thought almost exclusively in terms of the bimodal type of variation, with a normal majority and a hypersusceptible minority (ILSI, 1992). That model might be appropriate for noncarcinogenic effects (e.g., normal versus asthmatic response to SO_2), but it ignores a major class of variability vis-à-vis cancer (the continuous, "silent" variety), and it fails to capture even some bimodal cases in which hypersusceptibility might be the rule, rather than the exception (e.g., the poor-acetylator phenotype).

The magnitude and extent of human variability due to particular acquired or inherited cancer-susceptibility factors should be determined through molecular epidemiologic and other studies sponsored by EPA, the National Institutes of Health, and other federal agencies. Two priorities for such research should be

- To explore and elucidate the relationships between variability in each measurable factor (e.g., DNA adduct formation) and variability in susceptibility to carcinogenesis.
- To provide guidance on how to construct appropriate samples of the population for epidemiologic studies and risk extrapolation, given the influence of susceptibility variation on uncertainty in population risk and the possible correlations between individual susceptibility and such factors as race, ethnicity, age, and sex.

Results of the research should be used to adjust and refine estimates of risks to individuals (identified, identifiable, or unidentifiable) and estimates of expected incidence in the general population.

The population distribution of interindividual variation in cancer susceptibility cannot now be estimated with much confidence. Preliminary studies of this question, both biologic (Hattis et al., 1986) and epidemiologic (Finkel, 1987) have concluded that the variation might be described as approximately lognormal, with about 10% of the population being different by a factor of 25-50 (either more or less susceptible) from the median individual (i.e., the logarithmic standard deviation of the distribution is approximately 2.0). While the estimated standard deviation of a susceptibility distribution suggested by these studies is uncertain, in light of the biochemical and epidemiological data reviewed earlier in this chapter it is currently not scientifically plausible that the U.S. population is strictly homogeneous in susceptibility to cancer induction by cancer-causing chemicals. EPA's guidelines are silent regarding person-to-person variations in susceptibility, thereby treating all humans as identical, despite substantial evidence and theory to the contrary. This is an important "missing default" in the guidelines. EPA does assume (although its language is not very clear in this regard) that the median human has susceptibility similar to that of the particular sex-strain combination of rodent that responds most sensitively of those tested in bioassays, or susceptibility identical with that of the particular persons observed in epidemiologic studies. These latter assumptions are reasonable as a starting point (Allen et al., 1988), but of course they could err substantially in either direction for a specific carcinogen or for carcinogens as a whole.

The missing default (variations in susceptibility among humans) and questionable default (average susceptibility of humans) are related in a straightforward manner. Any error of overestimation in rodent-to-human scaling (or in epidemiologic analysis) will tend to counteract the underestimation errors that must otherwise be introduced into some individual risk estimates by EPA's current practice of not distinguishing among different degrees of human susceptibility.

Conversely, any error of underestimation in interspecies scaling will exacerbate the underestimation of individual risks for every person of above-average susceptibility. Therefore, EPA should increase its efforts to validate or improve the default assumption that the median human has similar susceptibility to that of the rodent strain used to compute potency, and should attempt to assess the plausible range of uncertainty surrounding the existing assumption. For further information, see the discussion in Chapter 11.

It can be argued, in addition, that EPA has a responsibility, insofar as it is practicable, to protect persons regardless of their individual susceptibility to carcinogenesis (we use *protect* here not in the absolute, zero-risk sense, but in the sense of ensuring that excess individual risk is within acceptable levels or below a de minimus level). It is unclear from the language in CAAA-90 Section 112(f)(2) whether the "individual most exposed to emissions" is intended to mean the person at highest risk when both exposure and susceptibility are taken into account, but this interpretation is both plausible and consistent with the fact that a major determinant of susceptibility is the degree of metabolism of inhaled or ingested pollutants and the resulting exposure of somatic and germ cells to carcinogenic compounds (i.e., two people of different susceptibilities will likely be "exposed" to a different extent even if they breathe or ingest identical ambient concentrations). Moreover, EPA has a record of attempting to protect people with a combination of high exposure and high sensitivity, as seen in the National Ambient Air Quality Standards (NAAQS) program for criteria air pollutants (e.g., SO_2, NO_x, ozone, etc.).

Therefore, EPA should adopt an explicit default assumption for susceptibility before it begins to implement those decisions called for in the Clean Air Act Amendments of 1990 that require the calculation of risks to individuals. EPA could choose to incorporate into its cancer risk estimates for individual risk (not for population risk) a "default susceptibility factor" greater than the implicit factor of 1 that results from treating all humans as identical. EPA should explicitly choose a default factor greater than 1 if it interprets the statutory language to apply to individuals with both high exposure and above-average susceptibility.[6] EPA could explicitly choose a default factor of 1 for this purpose, if it interprets the statutory language to apply to the person who is average (in terms of susceptibility) but has high exposure. Or, preferably, EPA could develop a "default distribution" of susceptibility, and then generate the joint distribution of exposure and cancer potency (in light of susceptibility), to find the upper 95^{th} or 99^{th} percentile of risk for use in a risk assessment. The distribution is the more desirable way of dealing with this problem, because it takes explicit account of the joint probability (which may be large or small) of a highly exposed individual who is also highly susceptible.

Many of the currently known individual determinants of susceptibility vary by factors of hundreds or thousands at the cellular level; however, many of these risk factors (see Appendix I-2) tend to confer excess risks of approximately a

factor of 10 on predisposed people, compared with "normal" ones. Although the total effect of the many such factors may cause susceptibility to vary upwards by more than a factor of 10, some members of the committee suggest that a default factor of 10 might be a reasonable starting point, if EPA wished to apply the statutory risk criteria (see Chapter 2) to the more susceptible members of the human population. Conversely, other members of the committee do not consider an explicit factor of 10 to be justified at this time. A 10-fold adjustment might yield a reasonable best estimate of the high end of the susceptibility distribution for some pollutants when only a single predisposing factor divides the population into normal and hypersusceptible people.

If any susceptibility factor greater than 1 is applied, the short-term practical effect will be to increase all risk assessments for individual risk by the same factor, except for chemical-specific risk estimates where there is evidence that the variation in human susceptibility is larger or smaller for that chemical than for other substances. Such a general adjustment of either the default factor or default distribution might become appropriate when more information becomes available about the nature and extent of interindividual variations in susceptibility.

Individual risk assessments may depart from the new default when it can be shown either that humans are systematically either more or less sensitive than rodents to a particular chemical or that interindividual variation is markedly either more or less broad for this chemical than for the typical chemical. Therefore, in the spirit of our recommendations in Chapter 6 and Appendixes N-1 and N-2, the committee encourages EPA both to rethink the new default in general and to depart from it in specific cases when appropriately justified by general principles the agency should articulate.

Although it is known that there are susceptibility differences among people due to such factors as age, sex, race, and ethnicity, the nature and magnitude of these differences is not well known or understood; therefore, it is critical that additional research be pursued. As knowledge increases, science may be able to describe differences in the population at risk and recognize these differences with some type of default or distribution, although caution will be necessary to ensure that broad *correlations* between susceptibility and age, sex, etc., are not interpreted as deterministic *predictions*, valid for all individuals, or used in areas outside of risk assessment without proper respect for autonomy, privacy, and other social values.

In addition to adopting a default assumption for the effect of variations in susceptibility on individual risk, EPA should consider whether these variations might affect calculations of *population risk* as well. Estimates of population risk (i.e., the number of cases of disease or the number of deaths that might occur as a result of some exposure) are generally based on estimates of the average individual risk, which are then multiplied by the number of exposed persons to obtain a population risk estimate. The fact that individuals have unique susceptibilities should thus be irrelevant to calculating population risk, except if ignoring

these variations *biases the estimate of average risk*. Some observers have pointed out a logical reason why EPA's current procedures might misestimate average risk. Even assuming that allometric or other interspecies scaling procedures correctly map the risk to test animals onto the "risk to the average human" (an assumption we encourage EPA to explore, validate, or refine), it is not clear *which* "average" is correctly estimated—the *median* (i.e., the risk to a person who has susceptibility at the 50^{th} percentile of the population distribution) or the *expected value* (i.e., the average individual risk, taking into account *all* of the risks in the population and their frequency or likelihood of occurrence).

If person-to-person variation in susceptibility is small or symmetrically distributed (as in a normal distribution), the median and the average (or mean) are likely to be equivalent, or so similar that this distinction is of no practical importance. However, if variation is large and asymmetrically distributed (as in a lognormal distribution with logarithmic standard deviation on the order of 2.0 or higher—see earlier example), the mean may exceed the median by roughly an order of magnitude or more.[7]

The committee encourages EPA to explore whether extrapolations made from animal bioassay data (or from epidemiological studies) at high exposures are likely to be appropriate for the median or for the average human, and to explore what response is warranted for the estimation and communication of population risk if the median and average are believed to differ significantly. As an initial position, EPA might assume that animal tests and epidemiological studies in fact lead to risk estimates for the *median* of the exposed group. This position would be based on the logic that at high exposures and hence high risks (that is, on the order of 10^{-2} for most epidemiologic studies, and 10^{-1} for bioassays), the effect of any variations in susceptibility within the test population would be truncated or attenuated. In such cases, any test animal or human subject whose *susceptibility* was X-fold higher than the median would face *risks* (far) less than X-fold higher than the median risk, because in no case can risk exceed 1.0 (certainty), and thus the effect of these individuals on the population average would not be in proportion to their susceptibilities. On the other hand, when extrapolating to ambient exposures where the median risk is closer to 10^{-6}, the full divergence between median and average in the general population would presumably manifest itself.

If, therefore, current procedures correctly estimate the median risk, then estimates of population risk would have to be increased by a factor corresponding to the ratio of the average to the median.

Other Changes in Risk-Assessment Methods

(1) Children are a readily identifiable subpopulation with its own physiologic characteristics (e.g., body weight), uptake characteristics (e.g., food consumption patterns), and inherent susceptibilities. When excess lifetime risk is the desired measure, EPA should compute an integrated lifetime risk, taking into account all relevant age-dependent variables, such as body weight,

uptake, and average susceptibility (for one example of such a computation, see Appendix C of NRDC, 1989). If there is reason to believe that risk is not linearly related to biologically effective dose, and if the computed risks for children and adults are found to be significantly different, EPA should present separate risk assessments for children and adults.

(2) Although EPA has tried to take account of interindividual variability in susceptibility for non-cancer effects (e.g., in standards for criteria air pollutants such as ozone or SO_2), such efforts have neither seen exhaustive nor part of an overall focus on variability. In particular, the "10-fold safety factor" used to account for interindividual variability when extrapolating from animal toxicity data has not been validated, in the sense that EPA is generally not aware how much of the human population falls within an order of magnitude of the median susceptibility for any particular toxic stimulus.

Although this chapter has focused on susceptibility to carcinogens, because this subject has received even less attention than that of susceptibility to noncarcinogens, the committee urges EPA to continue to improve its treatment of variability in the latter area as well.

(3) EPA has not sufficiently accounted for interindividual variability in biologic characteristics when it has used various physiologic or biologically based risk-assessment models. The validity of many of these models and assumptions depends crucially on the accuracy and precision of the human biological characteristics that drive them. In a wide variety of cases, interindividual variation can swamp the simple measurement uncertainty or the uncertainty in modeling that is inherent in deriving estimates for the "average" person. For example, physiologically based pharmacokinetic (PBPK) models require information about partition coefficients and enzyme concentrations and activities; Moolgavkar-Venzon-Knudson and other cell-kinetics models require information about cell growth and death rates and the timing of differentiation; and specific alternative models positing dose-response thresholds for given chemicals require information about ligand-receptor kinetics or other cellular phenomena. EPA has begun to collect data to support the development of distributions for the key PBPK parameters (such as alveolar ventilation rates, blood flows, partition coefficients, and Michaelis-Menten metabolic parameters) in both rodents and humans (EPA, 1988f). However, this database is still sparse, especially with respect to the possible variability in human parameters. EPA has developed point estimates for human PBPK parameters for 72 volatile organic chemicals, only 26 of which are on the list of 189 hazardous air pollutants covered in CAAA-90. For only five chemicals (benzene, *n*-hexane, toluene, trichloroethylene, and *n*-xylene) does EPA have any information on the presumed average and range of the parameters in the human population. It is perhaps noteworthy that in the one major instance in which EPA has revised a unit risk factor for a hazardous air pollutant on the

basis of PBPK data (the case of methylene chloride), no information on the possible effect of human variability was used (EPA, 1987d; Portier and Kaplan, 1989).

Even when the alternative to the default model hinges on a qualitative, rather than a quantitative, distinction, such as the possible irrelevance to humans of the alpha-2μ-globulin mechanism involved in the initiation of some male rat kidney tumors, the new model must be checked against the possibility that some humans are qualitatively different from the norm. Any alternative assumption might be flawed, if it turns out to be biologically inappropriate for some fraction of the human population. Finally, although epidemiology is a powerful tool that can be used as a "reality check" on the validity of potency estimates derived from animal data, there must be a sufficient amount of human data for this purpose. The sample size needed for a study to have a given power level *increase* under the assumption that humans are not of identical susceptibility.

When EPA proposes to adopt an alternative risk-assessment assumption (such as use of a PBPK model, use of a cell-kinetics model, or the determination that a given animal response is "not relevant to humans"), it should consider human interindividual variability in estimating the model parameters or verifying the assumption of "irrelevance." If the data are not available that would enable EPA to take account of human variability, EPA should be free to make any reasonable inferences about its extent and impact (rather than having to collect or await such data), but should encourage other interested parties to collect and provide the necessary data. In general, EPA should ensure that a similar level of variability analysis is applied to both the default and the alternative risk assessment, so that it can compare estimates of equal conservatism from each procedure.

Risk Communication

EPA often does not adequately communicate to its own decision-makers, to Congress, or to the public the variabilities that are and are not accounted for in any risk assessment and the implications for the conservatism and representativeness of the resulting risk numbers. Each of EPA's reports of a risk assessment should state its particular assumptions about human behavior and biology and what these do and do not account for. For example, a poor risk characterization for a hazardous air pollutant might say "The risk number R is a plausible upper bound." A better characterization would say, "The risk number R applies to a person of reasonably high-end behavior living at the fenceline 8 hours a day for 35 years." EPA should, whenever possible, go further and state, for example, "The person we are modeling is assumed to be of average susceptibility, but eats F grams per day of food grown in his backyard; the latter assumption is quite conservative, compared with the average."

Risk-communication and risk-management decisions are more difficult

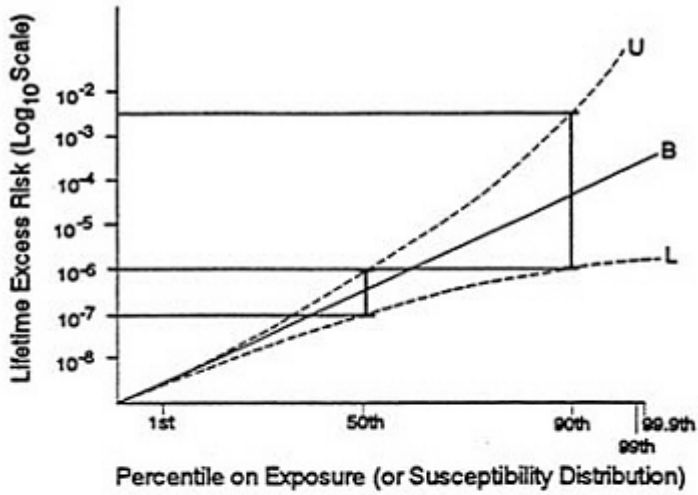
when, as is usually the case, there are both uncertainty and variability in key risk-assessment inputs. It is important, whenever possible, to separate the two phenomena conceptually, perhaps by presenting multiple analyses. For its full (as opposed to screening-level) risk assessments, EPA should acknowledge that all its risk numbers are made up of three components: the estimated risk itself (X), the level of confidence (Y) that the risk is no higher than X, and the percent of the population (Z) that X is intended to apply to in a variable population. EPA should use its present practice of saying that "the plausible upper-bound risk is X" only when it believes that Y and Z are both close to 100%. Otherwise, it should use statements like, "We are Y% certain that the risk is no more than X to Z% of the population," or use an equivalent pictorial representation (see Figure 10-2).

As an alternative or supplement to estimating the value of Z, EPA can and should try to present multiple scenarios to explain variability. For example, EPA could present one risk number (or preferably, an uncertainty distribution—see Chapter 9) that explicitly applies to a "person selected at random from the population," one that applies to a person of reasonably high susceptibility but "average" behavior (mobility, breathing rate, food consumption, etc.), and one that applies to a person whose susceptibility and behavioral variables are both in the "reasonably high" portion of their distributions.

Identifiability and Risk Assessment

Not all the suggestions presented here, especially those regarding variation in susceptibility, might apply in every regulatory situation. The committee notes that in the past, whenever persons of high risk or susceptibility have been identified, society has tended to feel a far greater responsibility to inform and protect them. For such identifiable variability, the recommendations in this section are particularly salient. However, interindividual variability might be important even when the specific people with high and low values of the relevant characteristic cannot currently be identified[8] Regardless of whether the variability is now identifiable (e.g., consumption rates of a given foodstuff), difficult to identify (e.g., presence of a mutant allele of a tumor-suppressor gene), or unidentifiable (e.g., a person's net susceptibility to carcinogenesis), the committee agrees that it is important to think about its potential magnitude and extent, to make it possible to assess whether existing procedures to estimate average risks and population incidence are biased or needlessly imprecise.

In contrast with issues involving average risk and incidence, however, some members of the committee consider the distribution of individual susceptibilities and the uncertainty as to where each person falls in that distribution to be irrelevant if the variation is and will remain unidentifiable. For example, some argue that people should be indifferent between a situation wherein their risk is determined to be precisely 10-5 or one wherein they have a 1% chance of being highly



- *Curve B* presents the best estimate of the relationship between exposure (or susceptibility) and risk [expressed in a scale relative to the rest of the population, not in absolute exposure (or susceptibility) units.]
- *Curve L* presents the 5th (or other lower) percentile of this relationship.
- *Curve U* presents the 95th (or other upper) percentile of this relationship.

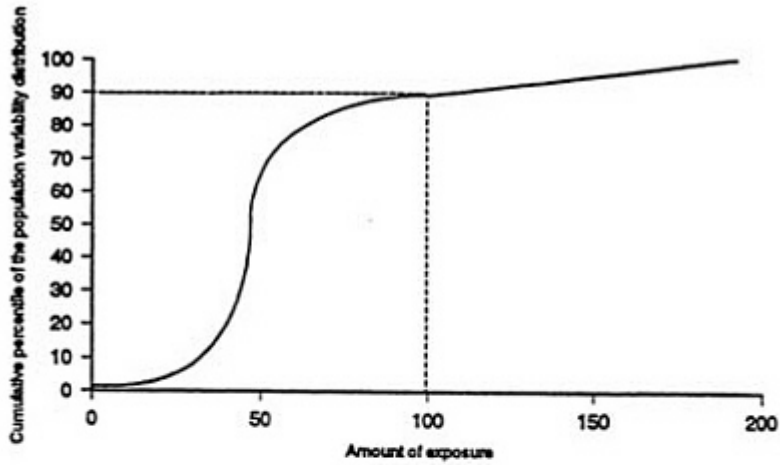
Thus, for this hypothetical example, the risk communicator could say:

"We are 90% certain that the risk to the person with median exposure is between 10^{-7} and 10^{-4}," AND/OR

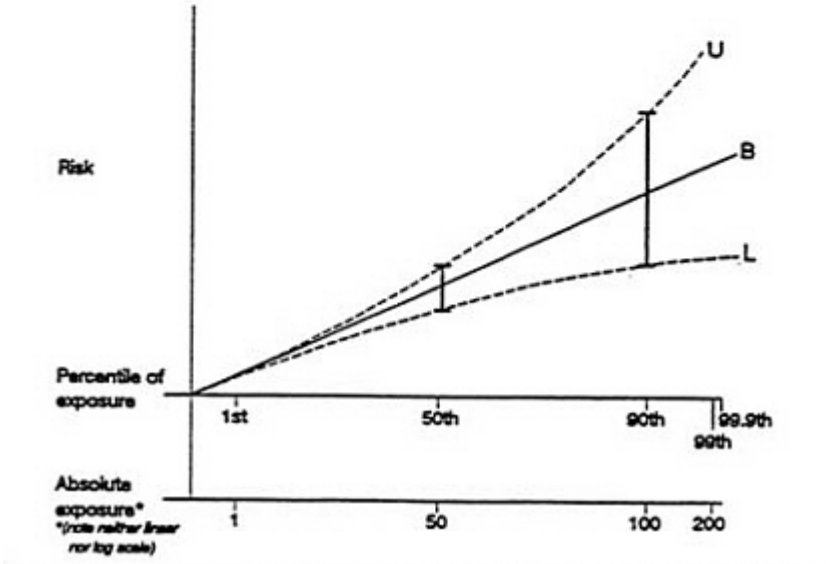
"We are 90% certain that the risk to the person with high (90th percentile) exposure is between 10^{-4} and 3×10^{-3}."

FIGURE 10-2 Communicating risk, uncertainty, and variability graphically.

Note: To translate from percentile-relative exposure to absolute exposure, you could add a second x-axis scale based on a figure as follows:



Thus, combining figures 1 and 2 gives you the 2 x-axes:



susceptible (with risk = 10^{-3}) and a 99% chance of being immune, with no way to know which applies to whom. In both cases, the expected value of individual risk is 10^{-5}, and it can be argued that the distribution of risks is the same, in that without the prospect of identifiability no one actually faces a risk of 10^{-3}, but just an equal chance of facing such a risk (Nichols and Zeckhauser, 1986).

Some of the members also argue that as we learn more about individual susceptibility, we will eventually reach a point where we will know that some individuals are at extremely high risk (i.e., carried to its extreme, an average individual risk of 10^{-6} may really represent cases where one person in each million is guaranteed to develop cancer while everyone else is immune). As we approach this point, they contend, society will have to face up to the fact that in order to guarantee that everyone in the population faces "acceptable" low levels of risk, we would have to reduce emissions to an impossibly low extent.

Other committee members reject or deem irrelevant the notion that risk is ultimately either zero or 1; they believe that, both for an individual's assessment of how foreboding or tolerable a risky situation is and for society's assessment of how just or unjust the distribution of risks is, the information about the unidentifiable variability must be reported—that it affects both judgments. To bolster their contentions, these members cite literature about the limitations of expected utility theory, which takes the view, contradicted by actual survey data, that the distribution of risky outcomes about their mean values should not affect the individual's evaluation of the situation (Schrader-Frechette, 1985; Machina, 1990), and empirical findings that the skewness of lotteries over risky outcomes matters to people even when the mean and variance are kept constant (Lopes, 1984). They also argue that EPA should maintain consistency in how it handles exposure variability, which it reports even when the precise persons at each exposure level cannot be identified; i.e., EPA reports the variation in air concentration and the maximal concentration from a source even when (as is usually the case) it cannot predict exactly where the maximum will occur. If susceptibility is in large part related to person-to-person differences in the amount of carcinogenic material that a person's cells are exposed to via metabolism, then it is essentially another form of exposure variability, and the parallel with ambient (outside-the-body) exposure is close. Finally, they claim that having agreed that issues of pure uncertainty are important, EPA (and the committee) must be consistent and regard unidentifiable variability as relevant (see Appendix I-3). Our recommendations in Chapter 9 reflect our view that uncertainty is important because individuals and decision-makers do regard values other than the mean as highly relevant. If susceptibility is unidentifiable, then to the individual it represents a source of uncertainty about his or her individual risk, and many members of the committee believe it must be communicated just as uncertainty should be.

Social-science research aimed at clarifying the extent to which people care about unidentifiable variability in risk, the costs of accounting for it in risk management, and the extent to which people want government to take such

variation and costs into account in making regulatory decisions and in setting priorities might be helpful in resolving these issues.

Findings And Recommendations

The committees findings and recommendations are briefly summarized below.

Exposure

Historically, EPA has defined the maximally exposed individual (MEI) as the worst-case scenario—a continuous 70-year exposure to the maximal estimated long-term average concentration of a hazardous air pollutant. Departing from this practice, EPA has recently published methods for calculating bounding and "reasonably high-end" estimates of the highest actual or possible exposures using a real or default distribution of exposure within a population. The new exposure guidelines do not explicitly define a point on this distribution corresponding to the highest expected exposure level of an individual.

- The committee endorses the EPA's use of bounding estimates, but only in screening assessments to determine whether further levels of analysis are necessary. For further levels of analysis, the committee supports EPA's development of distributions of exposure values based on available measurements, modeling results, or both. These distributions can also be used to estimate the exposure of the maximally exposed person. For example, the most likely value of the exposure to the most exposed person is generally the $100[(N - 1)/N]^{th}$ percentile of the cumulative probability distribution characterizing interindividual variability in exposure, where N is the number of persons used to construct the exposure distribution. This is a particularly convenient estimator to use because it is independent of the shape of the exposure distribution. The committee recommends that EPA explicitly and consistently use an estimator such as $100[(N - 1)/N]$, because it, and not a vague estimate "somewhere above the 90^{th} percentile," is responsive to the language in CAAA-90 calling for the calculation of risk to "the individual most exposed to emissions. …"

In recent times, EPA has begun incorporating into distributions of exposure assumptions that are based on a national average of years of residence in a home, as a replacement for its 70-year exposure assumption (e.g., an average lifetime). Proposals have been made for a similar "departure from defaults" for the time an individual spends at a residence each day, as a replacement for the 24 hours assumption. However, such analyses make the assumption that individuals move to a location of zero exposure when they change residences during their lifetime or leave the home each day. But, people moving from one place to another, whether it be changing the location of their residence or moving from the home to office, may vary greatly in their exposure to any one pollutant, from relatively

high exposures to none. Further, some exposures to different pollutants may be considered as interchangeable: moving from one place to another may yield exposures to different pollutants which, being interchangeable in their effects, can be taken as an aggregate, single "exposure." This assumption of interchangeability may or may not be realistic; however, because people moving from place to place can be seen as being exposed, over time to a mixture of pollutants, some of them simultaneously and others at separate times, a simplistic analysis of residence times is not appropriate. The real problem is, in effect, a more complex problem of how to aggregate exposure to mixtures as well as one of multiple exposures of varying level of intensities to a single pollutant. Thus, a simplistic analysis based on a simple distribution of residence times is not appropriate.

- EPA should use the mean of current life expectancy as the assumption for the duration of individual residence time in a high-exposure area, or a distribution of residence times which accounts for the likelihood that changing residences might not result in significantly lower exposure. Similarly, EPA should use a conservative estimate for the number of hours a day an individual is exposed, or develop a distribution of the number of hours per day an individual spends in different exposure situations. Such information can be gathered through neighborhood surveys, etc. in these high-exposure areas. Note that the distribution would correctly be used only for individual risk calculations, as total population risk is unaffected by the number of persons whose exposures sum to a given total value (if risk is linearly related to exposure rate).

  EPA has not provided sufficient documentation in its exposure-assessment guidelines to ensure that its point-estimation techniques used to determine the "high-end exposure estimate" (HEEE) when data are sparse reliably yield an estimate at the desired location within the overall distribution of exposure (which, according to these guidelines, lies above the 90^{th} percentile but not beyond the confines of the entire distribution).
- EPA should provide a clear method and rationale for determining *when* point estimators for the HEEE can or should be used instead of a full Monte Carlo (or similar) approach to choosing the desired percentile explicitly. The rationale should more clearly indicate how such estimators are to be generated, should offer more documentation that such point-estimation methods do yield reasonably consistent representations of the desired percentile, and should justify the choice of such a percentile if it differs from that which corresponds to the expected value of exposure to the "person most exposed to emissions".

Potency

EPA has dealt little with the issue of human variability in susceptibility; the limited efforts to date have focused exclusively on variability relative to noncarcinogenic

effects (e.g., normal versus asthmatic response to SO_2). The appropriate response to variability for noncancer end points (i.e., identify the characteristics of "normal" and "hypersusceptible" individuals, and then decide whether or not to protect both groups) might not be appropriate for carcinogenesis, in which variability might well be continuous and unimodal, rather than either-or.

- EPA, NIH, and other federal agencies should sponsor molecular epidemiologic and other research on the extent of interindividual variability in various factors that affect susceptibility and cancer, on the relationships between variability in each factor and in the health end point, and on the possible correlations between susceptibility and such covariates as age, race, ethnicity, and sex. Results of the research should be used to adjust and refine estimates of risks to individuals (identified, identifiable, or unidentifiable) and estimates of expected incidence in the general population. As this research progresses, the natural science and social science community should collaborate to explore the implications of any susceptibility factors that can be tested for or that strongly correlate with other genetic traits, so as to ensure that any findings are not misinterpreted or used outside of the environmental risk assessment arena without proper care.

Susceptibility

EPA does not account for person-to-person variations in susceptibility to cancer; it thereby treats all humans as identical in this respect in its risk calculations.

- EPA should adopt a default assumption for susceptibility before it begins to implement those decisions called for in the Clean Air Act that require the calculation of risks to individuals. EPA could choose to incorporate into its cancer risk estimates for individual risk a "default susceptibility factor" greater than the implicit factor of 1 that results from treating all humans as identical. EPA should explicitly choose a default factor greater than 1 if it interprets the statutory language to apply to an individual with high exposure and above-average susceptibility. EPA could explicitly choose a default factor of 1 for this purpose, if it interprets the statutory language to apply to an individual with high exposure but average susceptibility. Preferably, EPA could develop a "default distribution" of susceptibility, and then generate the joint distribution of exposure and cancer potency (in light of susceptibility) to find the upper 95^{th} percentile (or 99^{th} percentile) of risk for each risk assessment.

  EPA makes its potency calculations on the assumption that, on average, humans have susceptibility similar to that of the particular sex-strain combination of rodent that responds most sensitively of those tested in bioassays or susceptibility identical with that of the particular groups of persons observed in epidemiologic studies.

- EPA should continue and increase its efforts to validate or improve the default assumption that, on average, humans to be protected at the risk-management stage have susceptibility similar to that of humans included in relevant epidemiological studies, the most-sensitive rodents tested, or both.

  It is possible that ignoring variations in human susceptibility may cause significant underestimation of population risk, if both of two conditions hold: (1) current procedures to extrapolate results of laboratory bioassays or epidemiologic studies to the general population correctly map the observed risk in the test population to the human with *median* susceptibility, not to the expected value averaged over the entire general population; and (2) there is sufficient skewed variability in susceptibility in the general population to cause the expected value to exceed the median to a significant extent.
- In addition to continuing to explore the assumption that interspecies scaling (or epidemiologic extrapolation) correctly predicts average human susceptibility, EPA should investigate whether the average that is predicted corresponds to the median or the expected value. If there is reason to suspect the former is true, EPA should consider whether it needs to adjust its estimates of population risk to account for this discrepancy.

  Children are a readily identifiable subpopulation with its own physiologic characteristics (e.g., body weight), uptake characteristics (e.g., food consumption patterns), and inherent susceptibilities.
- If there is reason to believe that risk of adverse biological effects per unit dose depends on age, EPA should present separate risk estimates for adults and children. When excess lifetime risk is the desired measure, EPA should compute an integrated lifetime risk, taking into account all relevant age-dependent variables.

  EPA does not usually explore or consider interindividual variability in key biologic parameters when it uses or evaluates various physiologic or biologically based risk-assessment models (or else evaluates some data but does not report on this in its final public documents). In some other cases, EPA does gather or review data that bear on human variability, but tends to accept them at face value without ensuring that they are representative of the entire population. As a general rule, the larger the number of characteristics with an important effect on risk or the more variable those characteristics are, the larger the sample of the human population needed to establish confidently the mean and range of each of those characteristics.
- When EPA proposes to adopt an alternative risk-assessment assumption (such as use of a PBPK model, use of a cell-kinetics model, or the determination that a given animal response is "not relevant to humans"), it should consider human interindividual variability in estimating the model parameters or verifying

the assumption of "irrelevance." If the data are not available to take account of human variability, EPA should be free to make any reasonable inferences about its extent and impact (rather than having to collect or await such data), but should encourage other interested parties to collect and provide the necessary data. In general, in parallel to recommendation UAR4, EPA should ensure that a similar level of variability analysis is applied to both the default and the alternative risk assessment, so that it can compare equivalently conservative estimates from each procedure.

Risk Communication

EPA does not adequately communicate to its own decision-makers, to Congress, or to the public the variabilities that are and are not accounted for in any risk assessment and the implications for the conservatism and representativeness of the resulting risk numbers.

- EPA should carefully state in each risk assessment what its particular assumptions about human behavior and biology do and do not account for.

  For its full (as opposed to screening-level) risk assessments, EPA makes risk-communication and risk-management decisions more difficult when, as is usually the case, both uncertainty and variability are important.
- Whenever possible, EPA should separate uncertainty and variability conceptually, perhaps by presenting multiple analyses. EPA should acknowledge that all its risk numbers are made up of three components: the estimated risk itself (X), the level of confidence (Y) that the risk is no higher than X, and the percent of the population (Z) that X is intended to apply to in a variable population. In addition, rather than reporting both Y and Z, EPA can and should try to present multiple scenarios to explore and explain the variability dimension.

Notes

1. Some specialists in different fields often use the term "variability" to refer to a dispersion of possible or actual values associated with a particular quantity, often with reference to random variability associated with any estimate of an unknown (i.e., *uncertain*) quantity. This report, unless stated otherwise, will use the terms *interindividual variability, variability*, and *interindividual heterogeneity* all to refer to individual-to-individual differences in quantities associated with predicted risk, such as in measures of or parameters used to model ambient concentration, uptake or exposure per unit ambient concentration, biologically effective dose per unit exposure, and increased risk per unit effective dose.

2. This assumes that risk is linear in long-term average dose, which is one of the bases of the classical models of carcinogenesis (e.g., the LMS dose-response model using administered dose). However, when one moves to more sophisticated models of the dose-exposure (i.e., PBPK) and exposure-response (i.e., biologically motivated or cell-kinetics models) relationships, shorter averaging times become important even though the health endpoint may manifest itself over the long-term. For example, the cancer risk from a chemical that is both metabolically activated and detoxified *in*

vivo may not be a function of total exposure, but only of those periods of exposure during which detoxification pathways cannot keep pace with activating ones. In such cases, data on average long-term concentrations (and interindividual variability therein) may completely miss the only toxicologically relevant exposure periods.

3. As discussed above, in many cases variability that exists over a short averaging time may grow less and less important as the averaging time increases. For example, if on average, adults breathe 20m3 of air per day, then over any random 1-minute period, in a group of 1,000 adults there would probably be some (those involved in heavy exertion) breathing much more than the average value of 0.014 (m^3/min), and other (those asleep) breathing much less. Over the course of a year, however, the variation around the average value of 7300 m^3/yr would be much smaller, as periods of heavy exercise, sleep, and average activity "average out." On the other hand, some varying human characteristics do not substantially converge over longer averaging periods. For example, the daily variation in the amount of apple juice people drink probably mirrors the monthly and yearly variation as well—those individuals who drink no apple juice on a random day are probably those who rarely or never drink it, while those at the other "tail" of the distribution (drinking perhaps three glasses per day) probably tend to repeat this pattern day after day (in other words, the distribution of "glasses drunk per year" probably extends all the way from zero to 365 × 3, rather than varying narrowly around the midpoint of this range).

4. Similarly, the two persons might face equal cancer risks at exposures that were 10,000-fold different. However, an alternative definition, which would be more applicable for threshold effects, would be to call the difference in susceptibility the ratio of doses needed to produce the same effect in two different individuals.

5. The logarithmic standard deviation is equivalent to the standard deviation of the normal distribution corresponding to the particular lognormal distribution. If one takes the antilog of the logarithmic standard deviation, one obtains the "geometric standard deviation", or GSD, which has a more intuitively appealing definition: N standard deviations away from the median corresponds to multiplying or dividing the median by the GSD raised to the power N.

6. Moreover, existing studies of overall variations in susceptibility suggest that a factor of 10 probably subsumes one or perhaps 1.5 standard deviations above the median for the normal human population. That is, assuming (as EPA does via its explicit default) that the median human and the rodent strain used to estimate potency are of similar susceptibility, an additional factor of 10 would equate the rodent response to approximately the 85^{th} or 90^{th} percentiles of human response. That would be a protective, but not a *highly* conservative, safety factor, inasmuch as perhaps 10 percent or more of the population would be (much) more susceptible than this new reference point.

Inclusion of a default factor of 10 could bring cancer risk assessment partway into line with the prevailing practice in noncancer risk assessment, wherein one of the factors of 10 that are often added is meant to account for person-to-person variations in sensitivity.

However, if EPA decides to use a factor of 10, it should emphasize that this is a default procedure that tries to account for some of the interindividual variation in dose-response relationships, but that in specific cases may be too high or too low to provide the optimum degree of "protection" (or to reduce risks to "acceptable" levels) for persons of truly unusual susceptibility. Nor does it ensure that (in combination with exposure estimates that might actually correspond to a maximally exposed or reasonably high-end person) risk estimates are predictive or conservative for the actual "maximally-at-risk" person. In contrast, some persons of extremely high susceptibility might, as a consequence of their susceptibility, not face high exposures. It might also be the case that some risk factors for carcinogenesis also predispose those affected to other diseases from which it might be impossible to protect them.

7. For example, suppose the median income in a country was $10,000, but 5 percent of the population earned 25 times less or more than the median and an additional 1 percent earned 100 times less or more. Then the average income would be [(0.05)(400) + (0.05)(250,000) + (0.01)(100) + (0.01)(1,000,000) + (0.88)(10,000)] = $31,321, or more than three times the median income.

8. "Currently" is an important qualifier given the rapid increases in our understanding of the molecular mechanisms of carcinogenesis. During the next several decades, science will doubtless become more adept at identifying individuals with greater susceptibility than average, and perhaps even pinpoint specific substances to which such individuals are particularly susceptible.

11

Aggregation

Introduction

A recurring issue in quantitative risk assessment and quantitative risk characterization is the aggregation (and disaggregation) of separate but related causes and effects of risk. Questions about the aggregation of causes or agents differ somewhat from questions about the aggregation effects or end points, but the similarities are great enough for us to treat them together in this chapter. For example, people may be exposed to mixtures of compounds from a single stack, and each compound may be associated with an increase in the degree or probability of occurrence of one or more toxic end points; the situation can be further complicated by questions about synergy. In contrast, dose-response data are often available only on single end points in response to doses of single agents. How should we characterize and estimate the potential aggregate toxicity posed by exposure to a mixture of toxic agents?

The aggregation problem is simplified when all end points of concern are believed to have dose-response thresholds or no-adverse-effect levels. Under this restriction, "acceptable," "allowable," or "reference" doses are typically calculated by dividing empirically determined threshold estimates (such as no-observed-adverse-effect levels, NOAELs) by appropriate safety or uncertainty factors (Dourson and Stara, 1983; Layton et al., 1987; Barnes and Dourson, 1988; Lu, 1988; Shoaf, 1991). The risk-management goal for mixed exposures is generally to avoid exposures that exceed any of the relevant thresholds, while taking into account the possible joint effects of multiple agents. One strategy that has been implemented in environmental and occupational settings is to ensure

that the sum of all the ratios of incurred dose to acceptable dose relevant to a given end point total less than 1 (NRC, 1972a, 1989; OSHA, 1983; ACGIH, 1977, 1988; EPA, 1987a, 1988g; Calabrese, 1991; Pierson et al., 1991). That approach is based on an assumption that doses of different agents can be treated as roughly additive with regard to inducing the end point; this assumption is reasonably consistent with much of the experimental evidence on the joint actions of chemicals in mixtures.

Among the key problems associated with the general strategy is that the procedures currently used for defining acceptable exposures to systemic toxicants are rather crude. Proposals to incorporate more quantitative treatment of data and to focus on risk prediction without reference to thresholds (e.g., Crump, 1984; Dourson et al., 1985; Dourson, 1986) have not been widely adopted. The additivity assumption for systemic toxicants further complicates the crude approaches taken to identifying safe intakes of the components of a complex mixture. As an Environmental Protection Agency (EPA) technical support document (EPA, 1988g) comments, this use of the additivity assumption implies that,

> as the acceptable level is approached or exceeded, the level of concern increases linearly … and in the same manner for all mixtures [which is incorrect, because the estimates used to derive such recommended acceptable levels] do not have equal accuracy or precision, and are not based on the same severity of toxic effect. Moreover, slopes of dose-response curves in excess of [such levels] in theory are expected to differ widely. The determinations of accuracy, precision or slope are exceedingly difficult because of the general lack of toxicity data.

Despite its drawbacks, the crude additivity approach to the problem of aggregation of potential threshold effects has had relatively straightforward and uncontroversial regulatory applications.

Much more debate has focused on quantitative risk-assessment methods for end points assumed *not* to have threshold dose-response relationships, such as cancer. Particularly with regard to environmental exposures to multiple chemicals, risk-management decisions (e.g., cleanup criteria) tend to be driven by the estimated low-dose risk associated with exposure to materials that lead to assumed nonthreshold end points. This chapter focuses on aggregation of different risks and different types of risk attributable to integrated, multiroute exposure to multiple chemicals that are assumed to have nonthreshold effects.

Exposure Routes

Any comprehensive assessment of health risk associated with environmental exposure to any particular compound must consider all possible routes by which people might be exposed to that compound, even if expected applications in risk management are limited to some particular medium, such as air, or particular

source generator or category, such as a coke-oven facility. That is because compounds present in one environmental medium might be transferred to another at any time before exposure. The major routes of exposure are inhalation, ingestion, and dermal absorption. In the context of environmental exposures, *inhalation* pertains to uptake of compounds present in respired air during rest or activity both indoors and outdoors; *ingestion* refers to gastrointestinal absorption of compounds that are intentionally or unintentionally present in any ingested material, including water, liquid foods, mother's milk, solid foods (including crops and game), and soil; and *dermal absorption* refers to percutaneous uptake of compounds deposited on skin, including those present in water during showering, bathing, or recreational swimming. Assessments of exposure to a substance from a given source must account for all potentially important routes by which the substance might come into contact with people (or environmental biota, if an ecological impact assessment is being undertaken). For example, mercury emitted into air from an industrial smoke stack might be inhaled by nearby residents, but might pose an even greater health risk by the ingestion of bioconcentrated mercury in fish that are caught locally after mercury from the stack plume has been deposited onto lake water.

EPA has given the issue of integrated multiroute exposure considerable attention in the context of risk-assessment guidance for Superfund-related regulatory compliance (EPA, 1989a). For example, EPA suggested that assessment of the environmental fate and transport of compounds in ambient air address a range of issues as diverse as volatilization and occurrence in wild game (EPA, 1988h, 1989a,c,d,e). Additional information on multimedia transport and multiroute exposure assessments is available (Neely, 1980; Neely and Blau, 1985; Cohen, 1986; McKone and Layton, 1986; Allen et al., 1989; Cohen et al., 1990; McKone and Daniels, 1991; McKone, 1991, 1992).

Risk-Inducing Agents

Quantitative environmental risk assessment is often needed for exposure to multiple toxic agents, for example, in the context of hazardous-waste, drinking-water, and air-pollution control. The 1990 Amendments to the Clean Air Act in particular list 189 airborne pollutants of immediate regulatory concern that can be emitted singly or in combination from a variety of specified emission-source categories.

Over the last 2 decades, environmental remediation involving complex chemical mixtures has required general reviews of issues and cases of potential toxicity associated with concurrent exposure to multiple chemical agents (e.g., NRC, 1972a, 1980a,b, 1988a, 1989; EPA, 1988i; Goldstein et al., 1990; Calabrese, 1991). The earlier reviews supported the concept that toxicity predicted by dose additivity or concentration additivity was reasonably consistent with data on the joint action of acute toxicants (NRC, 1972a, 1980a,b; ACGIH, 1977;

EPA, 1987a). Although some cases of supra-additivity for acute toxicants are known, such as the synergistic interaction of organophosphate pesticide combinations in which one compound inhibits the detoxification of another compound, additivity has nevertheless been viewed as a reasonable expectation at the low doses at which detoxification enzymes are not expected to be saturated (NRC, 1988b; Calabrese, 1991).

The EPA Database on Toxic Interactions, as of 1988, covered 331 studies involving roughly 600 chemicals (EPA, 1988g). Most of the studies focused on the effects of two-compound mixtures on acute lethality; fewer than 10% examined chronic or lifetime toxicity. Less than 3% of all the studies reported clear evidence of a synergistic interaction—i.e., a "response to a mixture of toxic chemicals that is greater than that suggested by the component toxicities" (EPA, 1988g). However, EPA also concluded that in only one of 32 studies chosen as a 10% random sample of the 331 studies was the design and use of statistics "appropriate with the conclusion justified" (EPA, 1988g). As a consequence, EPA has asserted that

> given the quality and quantity of the available data on chemical interactions, few generalizations can be made concerning the likelihood, nature or magnitude of interactions. Most interactions that have been quantified are within a factor of 10 of the expected activity based on the assumption of dose addition (EPA, 1988g).

Results of the few detailed comparative studies in which *Salmonella*-mutation assays were applied to complex mixtures (kerosene-combustion particles, coalhydrogenation material, and heterocyclic amines from cooked food) are also generally consistent with approximate additivity of mutagenic potencies of constituents within complex mutagenic mixtures (Thilly et al., 1983; Felton et al., 1984; Schoeny et al., 1986).

Epidemiological evidence concerning the synergistic potential of human carcinogens (usually involving long-term cigarette-smoking) has been extensively reviewed (Saracci, 1977; Steenland and Thun, 1986; EPA, 1988g; NRC, 1988a,b; Kaldor and L'Abbé, 1990; Pershagen, 1990; Calabrese, 1991). Although no single mathematical expression is likely to give an accurate representation of joint effects, especially given the heterogeneity of human responses, the discussion here has often focused on whether responses are more clearly additive or multiplicative. The best-studied interactions (such as in joint exposure to tobacco and radon or tobacco and asbestos) suggest that a strictly additive model within the dose ranges studies may underestimate the true joint effects by a factor of 3-10. Results of epidemiological studies of joint exposure to radon progeny and cigarette smoke, for example, have been interpreted as showing an additive or possibly multiplicative interaction of the two agents with respect to the number of cancers induced and a synergistic decrease in latency period for tumor induction (NCRP, 1984; NRC, 1988a). The NRC (1988b) BEIR IV committee

concluded that results of epidemiological studies of smoking and nonsmoking uranium miners exposed to radon gas, particularly the large study by Whittemore and McMillan (1983), were consistent with a multiplicative effect of the combined agents.

The effects of asbestos exposure among workers who have a history of cigarette-smoking have been described (NRC, 1988a) as "one of the most current and well-recognized examples [based on epidemiological data] of how two distinct agents administered together can produce an increased incidence of [lung] cancer that is greater than that predicted from the administration of either agent alone [and that] is considered multiplicative by most investigators who have studied the problem." A study not cited by NRC of more than 1,600 British asbestos workers suggests an additive, rather than multiplicative, increase in relative risk after joint tobacco and asbestos exposure (Berry et al., 1985). Other investigators have also concluded that the overall evidence of multiplicative interaction of these agents is questionable (Saracci, 1977; Steenland and Thun, 1986).

Epidemiological detection of possible multiplicative action among human carcinogens is not surprising, given the large amount of experimental data on the action of cancer promoters in animals, including clear examples of supra-additive interaction (EPA, 1988g; Calabrese, 1991; Krewski and Thomas, 1992). Highly nonlinear, supra-additive synergistic interaction of some types of nongenotoxic cancer promoters with genotoxic agents is predicted by "biomechanistic" multistage models of carcinogenesis. In those models, increased cell replication can play a pivotal role either by directly increasing the rates of production of premalignant or malignant lesions, by amplifying the incidence of malignant lesions through stimulated growth of spontaneously occurring premalignant lesions, or both (Armitage and Doll, 1957; Moolgavkar and Knudson, 1981; Moolgavkar, 1983; Bogen, 1989; Cohen and Ellwein, 1990a,b; 1991; Ames and Gold, 1990a,b; Preston-Martin et al., 1990). From that mechanistic perspective, several nongenotoxic compounds are now thought to be capable of promoting carcinogenesis, both spontaneous and experimentally chemically induced, solely by increasing target-cell replication, a phenomenon that might have a threshold-like dose-response relation (Weisburger and Williams, 1983; Weisburger, 1988; Butterworth, 1989, 1990; Bogen, 1990b; IARC, 1991; Flamm and Lehman-McKeeman, 1991). EPA is considering formal recognition of such threshold carcinogens from the mechanistic perspective (e.g., EPA 1988g, 1991d), although these cases remain awkward to accommodate within EPA's currently-used 1986 general scheme for classifying potential chemical carcinogenicity (EPA, 1987a).

In general, both biological and statistical considerations make it difficult to rule out a nonthreshold mutation-related component of chemically induced carcinogenesis, and this effect might be dominant at low environmental exposures (Portier, 1987; Portier and Edler, 1990; Kopp-Schneider and Portier, 1991; Weinstein, 1991). For example, an increase in target-cell replication induced by some

nongenotoxic chemicals might have a low-dose, linear, nonthreshold dose-response relation. Alternatively, a broad distribution of thresholds within a highly heterogeneous human population might give rise to practical quasilinearity or superlinearity for low-dose promotional effects. Therefore, low-dose linearity has been recommended as a reasonable default assumption, even for agents known to increase cancer risk through nongenotoxic promotional mechanisms, in the absence of data establishing a pertinent, clearly defined, generally applicable threshold dose-response relation (Lutz, 1990; Perera, 1991). Under this default assumption, the mechanistic type of cancer-risk model and the classical multistage cancer-risk model both predict that small amounts of increased risk will be approximately linearly proportional to the risk associated with small combined doses of genotoxic or nongenotoxic carcinogens, or both, and that their joint action will be approximately additive (Gibb and Chen, 1986; NRC, 1988a; Brown and Chu, 1989; Krewski et al., 1989; Kodell et al., 1991b).

The general assumption of low-dose linearity for a presumed nonthreshold quantal end point (i.e., an end point observed only as present or absent), such as cancer occurrence before age 70, is equivalent to assuming $P = p + qD$, where P is the risk of such occurrence after a lifetime exposure at dose rate D, p is the background cancer risk by age 70, and q is the potency (increased risk per unit dose) for small values of D. Of interest is the aggregate increased probability P of cancer occurrence due to exposure to a low-dose environmental mixture of nonthreshold toxic agents. If the linear model is assumed for each of two such agents, and if an additional independent-action assumption is made that the agents act through statistically independent events to increase risk R, it follows that $P \grave{} q_1D_1 + q_2D_2$ for very small D_1 and D_2 (NRC, 1980b, 1988b; Berenbaum, 1989). A more general sum of potency-dose products has been used by EPA for approximating P in cases of exposure to a mixture of carcinogens (EPA, 1987a, 1988g). Appendix I-1 shows that the same general assumptions imply that a similar sum-of-products relation may be used to approximate the risk associated with mixtures of agents, each having one or more different end-point-specific effective dose rates. Multiple nonthreshold end points can be of interest in quantitative risk assessment, as discussed in more detail below.

Types of Nonthreshold Risk

Quantitative risk assessment can involve multiple toxic end points, as well as multiple toxic agents. In particular, toxic end points other than cancer might at some point also be assumed to have nonthreshold dose-response relations for public-health regulatory purposes. Furthermore, cancer is not a single disease, but a variety of neoplastic disorders with different characteristics that occur in different tissues of animals and humans at different times in the life history. Aggregate human cancer risk is often estimated from animal bioassay data that indicate statistically significant increases in dose-related risk of more than a

single tumor type (e.g., cancer of the lung and cancer of the kidney). Similarly, genetic, reproductive, and developmental risks can arise in multiple forms that are measured separately in toxicity assays (e.g., reduced fertility and incomplete ossification of some bone). The issues of aggregating risk of both multiple end points and multiple types of a given end point are discussed below. Both these aggregation problems can be addressed simultaneously by using Expression 6 in Appendix I-1, if independent actions and effects are assumed.

Cancer

The issue of how to use bioassay data that indicate dose-related effects for multiple tumor types is addressed by the EPA (1987a) cancer-risk guidelines as follows:

> To obtain a total estimate of carcinogenic risk, animals with one or more [histologically distinct] tumor sites or types showing significantly elevated … incidence should be pooled and used for [risk] extrapolation. The pooled estimates will generally be used in preference to risk estimates based on single types or sites.

If different tumor types observed to have increased incidences are known to occur in a statistically independent fashion within and among the bioassay animals tested, this EPA-recommended procedure leads to inconsistently biased estimates of aggregate potency or risk because, under the independence assumption, the pooled tumor-incidence data may randomly exclude relevant information (Bogen, 1990a). For potency estimates based on classical multistage models, that statistical problem is avoided if aggregate potency is estimated as the sum of tumor-type-specific potencies (Bogen, 1990a). If the latter approach is used, then the aggregate increased risk P of incurring one or more tumor types at a very low dose can be estimated from Expression 7 in Appendix I-1 (for one carcinogen). The type-specific potencies are uncertain quantities (one reason is that they are generally estimated from bioassay data), so appropriate procedures must be used for summation.

This alternative (Expression 7 in Appendix I-1) to EPA's procedure for estimating aggregate cancer potency depends on the validity of the assumption that different tumor types occur independently within individual bioassay animals. If substantial interanimal heterogeneity exists in susceptibility to cancer, or if tumor types are positively correlated, the occurrence of multiple tumor types would be expected to cluster in the more susceptible individuals. Although some significant tumor-type associations have been identified in some species, they have tended to involve a relatively small number of tumor types (see Appendix I-2).

Appendix I-2 summarizes an investigation of independence in interanimal tumor-type occurrence in a subset of the National Toxicology Program (NTP) 2-year

cancer-bioassay data, which has been used by EPA as the basis for quantifying the potency of most chemical carcinogens. Separate analyses were conducted for four sex-species combinations (male and female mice, male and female rats) by using control-animal data from 61 rat studies and 62 mouse studies and treated-animal data from a subset of studies in which there were significant increases in multiple tumor types. Correlations in the occurrence of pairs of tumor types in individual animals were evaluated. Little evidence was found of tumor-type correlation for most of the tumor-type pairs in control and treated mice and rats. Some tumor-type pairs were statistically significantly (and generally negatively) correlated, but in no case was the correlation large. These findings indicate that a general assumption of statistical independence of tumor-type occurrences within animals is not likely to introduce substantial error in assessing carcinogenic potency from NTP rodent-bioassay data.

Other Nonthreshold End Points

Two major categories of possible nonthreshold toxicity other than cancer that may often be relevant in quantitative risk assessment are genetic mutation (which might be caused by material that reaches and damages gonadal DNA) and developmental and reproductive toxicity (such as developmental neurotoxicity of lead). In general, however, if both dose-response linearity at low doses and independent dose induction of these effects are assumed, then they may also be incorporated with cancer into the general additive strategy already discussed. The extent to which those assumptions might apply to genetic toxicity and reproductive and developmental toxicity is considered below.

Genetic Effects

Mutagenic agents can cause detrimental inherited effects with an important genetic component, such as clinically autosomal dominant and recessive mutations, X-linked mutations, congenital birth defects, chromosomal anomalies, and multifactorial disorders of complex origin. Inherited genetic effects other than complex multifactorial effects have been found to occur spontaneously in roughly 2% of all liveborn people, appearing either at birth or thereafter; about 40-80% often involve chromosomal anomalies or dominant or X-linked mutations ("CADXMs") (Mohrenweiser, 1991). In addition, more than 25% of all spontaneous abortions are thought to be due to genetic defects, the majority involving CADXMs (Mohrenweiser, 1991). Rates of those genetic effects are known to be increased in animals by exposure to environmental agents, such as ionizing radiation (which also causes cancer); furthermore, the risks of both genetic and cancer end points associated with low doses of ionizing radiation are currently modeled as being increased above background in linear proportion to dose (NRC, 1972b, 1980c, 1990b; NCRP, 1989; Favor, 1989; Sobels, 1989; Vogel, 1992).

Exposure of experimental animals to mutagenic chemicals can also cause some of these genetic effects, although specific characteristics of chemically induced genetic damage appear to differ in some ways from those induced by irradiation, e.g., in the fraction of dominant versus recessive specific-locus effects (Ehling and Neuhauser, 1979; Lyon, 1985; Favor, 1989; Rhomberg et al., 1990).

Experimental data are not all consistent with a linear nonthreshold dose-response relation for genetic end points induced by either chemicals or ionizing radiation (ICPEMC, 1983a; Sobels, 1989). Chemical mutagenesis, in particular, involves many potentially nonlinear and threshold processes, such as transport of reactants, metabolic activation and deactivation, DNA repair, and chemically induced functional change and lethality (ICPEMC, 1983a). However, it is difficult (if not impossible) to show experimentally that a complex, inherently statistical biological response does not differ from background (ICPEMC, 1983a). In light of such complexities, several National Research Council committees (NRC, 1975, 1977, 1983b) have concluded that the linear nonthreshold dose-response assumption used for ionizing radiation is also a reasonable default hypothesis for mutagenic chemicals. That conclusion reflects the fact that "if an effect can be caused by a single hit, a single molecule, or a single unit of exposure, then the effect in question cannot have a threshold in the dose-response relationship, no matter how unlikely it is that the single hit or event will produce the effect." It has been similarly concluded that a linear nonthreshold dose-response relation is a reasonable default assumption for chemical mutagens (Ehling and Neuhauser, 1979; ICPEMC, 1983a,b; Lyon, 1985; Ehling, 1988; Favor, 1989; Sobels, 1989; Rhomberg et al., 1990).

Such support of a default assumption of nonthreshold linearity in induced genetic risk has highlighted the uncertainty that exists in quantitative assessment of the total genetic risk to humans associated with exposure to ionizing radiation or genotoxic chemicals. That uncertainty, due particularly to problems in estimating possible increases in rates of human genetic disease, has led some to conclude that realistic assessment of total genetic risk associated with environmental exposure will not soon be possible (NRC, 1990b; Mohrenweiser, 1991; Vogel, 1992). The degree of uncertainty varies greatly among different end points, but dose-response data for mutations in mice, supplemented by corresponding estimates of human spontaneous incidence rates, appear to provide a basis for reasonable quantitative risk assessment for some genetically simple and straightforward end points, such as those involving CADXMs (NRC, 1990b; Mohrenweiser, 1991; Vogel, 1992).

In 1986, EPA adopted guidelines for mutagenicity risk assessment that do not specifically endorse a linear nonthreshold default assumption. Rather, they state that EPA "will strive to use the most appropriate extrapolation models for risk analysis" and "will consider all relevant models for gene and chromosomal mutations in performing low-dose extrapolations and will chose the most appropriate model" (EPA, 1987a). The 1986 guidelines committed EPA to "assess

risks associated with all genetic end points" to the greatest extent possible when data are available, with risk to be "expressed in terms of the estimated increase of genetic disease per generation, or the fractional increase in the assumed background spontaneous mutation rate of humans." In pursuit of methods to implement the goals of its guidelines, EPA sponsored a major effort concerning genetic-risk assessment for the direct-acting mutagen ethylene oxide (Dellarco and Farland, 1990; Dellarco et al., 1990; Rhomberg et al., 1990). But EPA does not now routinely perform quantitative assessments of genetic risk posed by chemical mutagens in the environment as part of any of its regulatory programs.

EPA's 1986 guidelines are nonspecific not only regarding particular methods to be used by the agency for estimating mutagenic risk, but also regarding how such risk might be aggregated with risks estimated for other end points, such as cancer. The suggested measures of genetic risk in the guidelines cannot readily be aggregated with EPA's commonly used measures of increased cancer risk to individuals or populations. However, individual genetic risk could be expressed as increased lifetime risk of expression of a serious inherited genetic end point in a person whose parents were both exposed from birth to a given relevant compound at a given effective dose rate. And addition of such a predicted risk to a corresponding magnitude of predicted somatic (cancer) risk would be appropriate under assumptions of low-dose linearity and independence as discussed above and in Appendix I.

Risk assessments of ionizing radiation provide precedents for the simple addition of quantitative estimates of genetic and cancer risk (e.g., Anspaugh and Robison, 1968; ICRP, 1977a,b, 1984, 1985). However, EPA has made no systematic effort to consider the combination of mutagenic and cancer risks. In the context of setting radiological National Emission Standards for Hazardous Air Pollutants (NESHAPs), the agency's Office of Radiation Programs made a substantial effort to describe quantitative risk estimates for both cancer and genetic end points (EPA, 1989b). However, the genetic risk factors were not used later in EPA's corresponding quantitative radiologic-risk assessments for radioactive air contaminants (EPA, 1989b), nor are they considered in current EPA guidance on how to calculate preliminary Superfund remediation goals for radionuclides at hazardous-waste sites (EPA, 1991f).

The importance of considering a quantitative combination of genetic and cancer end points depends on the ratio of genetic-to-cancer potency of any given chemical. If the ratio is much less than 1, genetic-risk assessment of the chemical is probably unwarranted, because it is likely to have little impact on regulatory action. For example, the upper-bound estimate of the potency of ethylene oxide (ETO) to produce heritable translocations (HTs) in children of exposed men was recently estimated to be equivalent to 0.00066 per part of ETO per million parts of air continuously inhaled. This estimate was based on an EPA analysis that applied a linearized multistage extrapolation model to dose-response data on HT induction in mice; a 21-day critical exposure period was assumed to

be potentially damaging to human males (Rhomberg et al., 1990). In contrast, EPA had previously estimated ETO's cancer potency to be 0.19 per part of ETO per million part of air continuously inhaled over a lifetime—a value almost 290 times its estimated HT potency (EPA, 1985c). The genetic risk associated with ETO could not therefore constitute a substantial fraction of the genetic-pluscancer risk unless HT represented a very small fraction (e.g., less than 1/290) of all reasonably quantifiable ETO-induced genetic end points. This appears to be unlikely, given that HTs constitute between about 5% and 10% of CADXMs (ICPEMC, 1983b).

Reproductive/Developmental Risks

There are continuing concerns about the adequacy of current approaches (threshold, linear, nonlinear, BD, etc., described in Chapter 4) to characterize the risks associated with potential reproductive and developmental hazards (Barnes and Dourson, 1988; Mattison, 1991). Particular questions remain regarding thresholds. Although threshold mechanisms might seem plausible, the estimation of an upper limit to ensure that doses are safe depends heavily on available methods of study and measurement and our knowledge of organ- and tissue-specific repair mechanisms. The issue merits continued consideration. This issue is also discussed in the NRC report entitled *Seafood Safety* (NRC, 1991b).

The current and proposed EPA guidelines concerning reproductiveand developmental-toxicity risk assessment are based on the controversial assumption that chemical induction of reproductive or developmental toxicity generally has a true or practical threshold dose-response relationship. As noted by EPA (1991a), such thresholds might differ among exposed people, and EPA has traditionally accommodated such interindividual variability by using an extra uncertainty factor or safety factor of 10, whose adequacy remains to be established.

Measures And Characteristics Of Risk

Overall Characterization Goals

An essential component of risk characterization is the aggregation of different measures and characteristics of risk; the risk assessor must communicate measures and characteristics of predicted risk in ways that are useful in risk management. The technical aspects of risk aggregation and characterization cannot and should not be separated from the design of useful, politically responsible, and legally tenable criteria of risk acceptability, because such criteria must generally be based on risk characterizations that follow some standard format, and the format must accommodate the criteria. As new, more sophisticated approaches to risk assessment and characterization are proposed—such as the incorporation of integrated uncertainty and variability analysis—the corresponding

more complicated criteria for risk acceptability have not been agreed on. It is therefore appropriate to establish as an interim goal of risk characterization the adoption of a format that includes a summary of predicted risk that is accurate, comprehensive, easily understood, and responsive to a wide array of public concerns about risk. The format should include the magnitude and uncertainty of estimated population risk (that is, predicted incidence) as well as individual risk, the uncertainty of estimates of costs and competing risks inherent in alternative risk-management options, the degree to which estimated risks might vary among exposed individuals, and the time frame of risks imposed.

Consistency in Characterization: Example of Aggregation of Uncertainty

To the extent that a given aggregated characteristic of a risk assessment, such as uncertainty, is addressed in an overall characterization of predicted risk, it should be determined with a consistent approach to estimates of the magnitudes of the components considered (e.g., ambient concentration, uptake, and potency). In the case of uncertainty aggregation, such consistency will come about through a rigorous, fully quantitative approach (see Chapter 9). But such a fully quantitative approach might be deemed impractical; for example, quantification of subjective probability judgments in the assessment might be considered difficult or misleading. A screening-level alternative to a fully quantitative approach to uncertainty aggregation is to use a qualitative or categorical approach that describes, in narrative or tabular form, the impact of each component of the analysis on each aspect of predicted risk. However, an exclusively qualitative, categorical approach is generally impractical because it fails to communicate effectively the fundamental quantitative conclusions of the risk analysis in terms that are of direct use to risk managers.

Thus, the approach to uncertainty aggregation most often used has been a semiquantitative approach incorporating specific key assumptions whose merits and impact are discussed verbally. The difficulty with this approach lies in ensuring that resulting semiquantitative characteristics are properly interpreted and communicated. For example, it would be illogical and potentially misleading to characterize a final risk estimate as a "plausible upper bound" on risk, if it were derived by aggregating component-specific point estimates that represent a mixture of best estimates and statistical upper confidence limits. That is particularly true if the components for which *best* estimates are used are also the components known to be the most uncertain among those considered. When, for example, risk is modeled as a simple product of estimated quantities (such as concentration, potency, etc.) a great deal of conservatism is lost whenever a best estimate is used in place of a far larger corresponding upper-bound value (and little conservatism is gained by using an upper-bound value if it is close to the corresponding best estimate). Thus, if a semiquantitative approach is to be used,

the only way to obtain a meaningful "upper-bound" point estimate of risk from component-specific point estimates would be to base the "upper-bound" point estimate *entirely* on "upper-bound" estimates of *all* the component quantities. This point is illustrated by the following example involving EPA's cancer-risk guidelines.

The EPA guidelines for cancer-risk characterize the estimate produced by following the guidelines as a "plausible upper bound" on increased cancer risk. Such a risk estimation will generally involve a pertinent set of animal bioassay data, an animal-cancer potency estimate, and an interspecies dose-scaling factor. According to the 1986 guidelines, the risk assessment is to be based on the data showing the most sensitive response (i.e., that give the highest estimated potency value or set of related values), and the animal-cancer potency value used is a statistical upper confidence limit of potency estimated from the animal-bioassay data set selected. The guidelines specify a dose-scaling factor—based on what was intended by EPA to be a deliberately conservative assumption that carcinogenic doses are equivalent between species if they are expressed as daily mass per unit of body surface area. Recently, EPA (1992e) proposed adopting a new scaling factor that is somewhat less conservative because this new factor appears to be close to a "best" estimate of what the factor might actually be. However, EPA (1992e) noted that

> Although scaling doses by [the newly proposed factor] characterizes the trend [relating epidemiologically based human-cancer potencies with corresponding experimentally determined ones for animals] fairly well, individual chemicals may deviate from this overall pattern by two orders of magnitude or more in either direction. … The proposed scaling [approach] … represents a best guess … surrounded by an envelope of considerable uncertainty. … [It] is intended to be…an unbiased projection; i.e., it is to be thought of as a "best" estimate rather than one with some conservatism built in … [such] as a "safety factor" or other intentional bias designed to "err on the side of safety."

A similarly large degree of uncertainty associated with interspecies dose scaling was also indicated in a recent reassessment of uncertainty pertaining to interspecies extrapolation of acute toxicity (Watanable et al., 1992). Other studies (Raabe et al., 1983; Kaldor et al., 1988; Dedrick and Morrison, 1992) provide evidence that a milligram-per-kilogram-per-lifetime dose metric may be roughly equivalent across species. These studies compare human carcinogenicity and animal carcinogenicity for alkylating or radioactive agents (administered for therapeutic purposes in the case of humans). Dose-scaling uncertainty may thus be substantially far greater than that associated with parameter-estimation error for cancer potency in bioassay animals and be at least as great as that associated with the selection of a bioassay data set for analysis. EPA's proposed dose-scaling policy would therefore be an exception to its reasonably consistent practice of using component-specific upper bounds when semiquantitative aggregation of uncertainty is used to derive a "plausible upper bound" on increased risk. The most

straightforward way to obtain such an upper-bound dose-scaling factor would be to calculate it directly from the best available relevant empirical data that relate epidemiologically based human-cancer potencies to corresponding experimentally determined animal-cancer potencies (e.g., Raabe et al., 1983; Allen et al., 1988; Kaldor et al., 1988; Dedrick and Morrison, 1992). An uncertainty distribution for the scaling factor could also readily be developed from these data, and an appropriate summary statistic chosen explicitly from this distribution, rather than by fiat and without reference to uncertainty (see, for example, Watanabe et al., 1992).

Uncertainty and Variability

We have deliberately treated these two concepts separately up to this point in the report, because we view them as conceptually quite different even though they share much of the same terminology (e.g., "upper confidence limit," "standard deviation"). Indeed, as emphasized in Chapters 9 and 10, the realms of uncertainty and variability have fundamentally different ramifications for science and judgment: uncertainty forces decision-makers to judge how *probable* it is that risks will be overestimated or underestimated for every member of the exposed population, whereas variability forces them to cope with the *certainty* that different individuals will be subjected to risks both above and below any reference point one chooses.[1]

Thus, any criticism that EPA has assessed or managed a risk too "conservatively" needs to consider and explain which type of conservatism is being decried. The use of a plausible but highly conservative scientific model, if it imposes large costs on society or the regulated community, can throw into question whether it is wise to be "better safe than sorry." The attempt to provide protection to persons at the "conservative" end of a distribution of exposure or risk, in contrast, determines who ends up with what degree of safety and thus requires a different decision calculus. In particular situations, either uncertainty or variability (or perhaps both) might be handled "conservatively." For example, society might in one case determine that the marginal costs of protecting individuals with truly unusual hypersusceptibility were too large relative to the costs of protecting only the majority, but might still choose to assess the risk to each group in a highly conservative manner. In another case, society might view the central tendency of an uncertain risk as an appropriate summary statistic, yet deem it important to extend protection to individuals whose risks are far above the central tendency with respect to the varied risks across the population.

On the other hand, this risk management distinction between uncertainty and variability should not blind people to a central fact of environmental health risk assessment: that in general, risks are both uncertain and variable simultaneously. In the prototypical hazardous air pollutant risk assessment case, one can think of the source exposing each nearby resident to a different ambient

concentration of each emitted pollutant; each of these concentration values is made still more variable by the unique activity patterns, uptake parameters, and susceptibility of each individual. Simultaneously, each of these "individualized" parameters is either hard to measure or impossible to model with certainty (or both), and all of the "generalized" parameters (such as the inherent carcinogenic potency of each substance) are also surrounded by uncertainty. In sum, the source does not impose "a risk"—it imposes a *spectrum* of individual risks, *each* of which can only be completely described as a probability distribution rather than a single number.

Elsewhere in the report, we have commented on two aspects of the challenge of assessing variable and uncertain risks: communicating them correctly and comprehensively (see the findings and recommendations for this chapter), and describing how to relate variability to uncertainty in order to explicitly target risk management to the desired members of the population (average, "high-end," maximally at risk, etc.) in light of the uncertainty (again, see the findings and recommendations for this chapter).

Here, we briefly mention two additional complications that arise because uncertainty and variability work in tandem. We make no specific recommendations regarding either issue, because we feel EPA analysts and other risk assessors need flexibility to account for these technical problems as they gradually improve their treatment of the separate phenomena of uncertainty and variability. Nevertheless, it is important to keep in mind two other relationships between these phenomena:

(1) *Variability in one quantity can contribute to uncertainty in another*. The most relevant example of this general phenomenon involves the influence of variability in a quantity on the uncertainty in its mean. As mentioned in the introduction to Chapter 10, one way to deal with interindividual variability is to substitute the average value of the varying quantity, although this does preclude conducting analyses that are meaningful at the individual level. However, even this short-cut is not without additional complications, because the new parameter (the population average value of the variable quantity) may be rather uncertain if the variability is substantial. Although the central limit theorem states that the uncertainty in the mean is inversely proportional to the number of observations made, when the quantity varies by orders of magnitude, even "large" data sets (tens or even hundreds of observations) may not be sufficient to pin down the mean with the precision desired. A group of 1000 workers observed in an epidemiologic study, for example, may have an *average* susceptibility to cancer significantly greater or less than the true mean of the entire population, if by chance (or due to a systematic bias) the occupational group has slightly more or slightly fewer outliers (particularly those of extremely high susceptibility) than the overall population. In such cases, estimates of potency or population incidence drawn from the worker study may be overly "conservative" (or insufficiently so).

(2) *The amount of variability is generally itself an uncertain parameter* . There are at least three factors that work to complicate the estimation of variability. Thus, risk assessment parameters that attempt to summarize variability (either as inputs to other calculations or as the output for risk management or communication) should be regarded as uncertain unless these three factors are deemed unimportant: (1) "double-counting" and overestimation of variability may occur when error-prone measurements are made—these errors will tend to make the extremes in the population seem more divergent than they truly are; (2) even when measurements are perfect, the amount of variability cannot be perfectly determined from any single data set—random parameter uncertainty introduces the possibility that by chance, the population observed might be inherently less or more variable than the entire population; and (3) there may be "model uncertainty" in deciding what kind of probability distribution to fit to variable observations, and hence statistics such as the standard deviation or the upper confidence limit might be in error if they apply to a distribution that does not precisely describe the actual variability.

In sum, EPA should realize that estimates of variability themselves may be too large or too small—if "conservatism" is crucial, it may make sense to take account of this impreciseness of variability as well as taking account of variability itself (e.g., if fish consumption is deemed to be lognormal with a standard deviation somewhere between $(x - \delta)$ and $(x + \delta)$, it might be appropriate to use an upper confidence limit for fish consumption that is in turn based on the larger of the two estimates of variability, $x + \delta$.

Aggregation of Uncertainty and Variability

To the extent that both uncertainty and interindividual variability (that is, heterogeneity or differences among people at risk) are addressed quantitatively with separate input components (e.g., ambient concentration, uptake, and potency) for aggregation into an assessment of risk, the distinction between uncertainty and variability ought to be maintained rigorously throughout the analytic process, so that uncertainty and variability can be distinctly reflected in calculated risk. If no distinction were made between uncertainty-related and heterogeneity-related distributions associated with inputs to a given risk calculation, then whatever distribution might be obtained as a characteristic of risk would necessarily reflect risk to an individual selected at random from the exposed population (Bogen and Spear, 1987). This restricted result would render such analyses less useful for environmental regulatory purposes, in light of the tendency to focus substantial regulatory attention on increased risk to highly sensitive or highly exposed members of the population.

Another advantage of distinguishing between uncertainty and variability is that it permits one to estimate the uncertainty in the risk to the individual who is "average" with respect to all characteristics that are heterogeneous among individuals

at risk, and the latter risk may be used to estimate uncertainty in predicted population risk or number of cases (Bogen and Spear, 1987). Technical issues that arise in aggregating uncertainty and interindividual variability for the purpose of calculating estimated individual and population risk are described in Appendix I-3.

Findings And Recommendations

Multiple Routes of Exposure

Although the Clean Air Act Amendments of 1990 do not specifically refer to multiple exposure pathways, EPA has routinely considered multiple exposure routes in regulatory contexts, such as Superfund, that logically concern source-specific pollutants that might transfer to other media before human exposure.

- Health-risk assessments should generally consider all possible routes by which people at risk might be exposed, and this should be done universally for compounds regulated by EPA under the Clean Air Act Amendments of 1990. The agency's risk-assessment guidance for Superfund-related regulatory compliance (EPA, 1989a) can serve as a guide in this regard, but EPA should take advantage of new developments and approaches to the analysis of multimedia fate and transport data. This will facilitate systematic consideration of multiroute exposures in designing and measuring compliance with Clean Air Act requirements.

Multiple Compounds and End Points

When aggregating cancer risk associated with exposures to multiple compounds, EPA adds the risk related to each compound in developing its risk estimate. That is appropriate when the only risk characterization desired is a point estimate used for screening-level analysis. However, if a quantitative uncertainty characterization is desired, simple addition of upper confidence limits may not be appropriate.

- EPA should consider using appropriate statistical (e.g., Monte Carlo) procedures to aggregate cancer risks from exposure to multiple compounds if a quantitative uncertainty characterization is desired.

EPA currently uses a specific procedure when analyzing animal bioassay data involving the occurrence of multiple tumor types (e.g., lung, stomach, etc.) to estimate the total cancer risk associated with exposure to a single compound. In this procedure EPA adds the numbers of animals with tumor types that are significantly increased above control levels, such that an animal with multiple tumor types counts the same as one with a single tumor type. This procedure does not allow full use of the data available and can overestimate or underestimate total cancer risk.

- When analyzing animal bioassay data involving the occurrence of multiple tumor types, EPA should use the following default procedure. Cancer potencies should first be separately estimated for each tumor type involved with the procedure normally used in the case of bioassays involving a single tumor type. The type-specific potencies should then be added as upper bounds or using appropriate statistical (e.g., Monte Carlo) methods. This procedure should be used unless specific data indicate that occurrence of the different tumor types within individual animals are significantly correlated.

Genetic Effects

Current EPA guidelines do not clearly state a default option of nonthreshold low-dose linearity for genetic effects that can be reasonably estimated for quantitative risk assessment.

- EPA's guidelines should clearly state a default option of nonthreshold low-dose linearity for genetic effects on which adequate data (e.g., data on chromosomal aberrations or dominant or X-linked mutations) might exist. This default option allows a reasonable quantitative estimate of, for example, first-generation genetic risk due to environmental chemical exposure.

Reproductive and Developmental Toxicants

While EPA is increasing its use of the benchmark dose, it still uses a threshold model in its proposal for regulation for reproductive and developmental toxicants. Although the threshold model is generally accepted for these toxicants, it is not known how accurately it predicts human risk. Current evidence on some toxicants, most notably lead and alcohol, does not unequivocally demonstrate any "safe" threshold and thus has raised concerns that the threshold model might only reflect the limits of current scientific knowledge, rather than the limits of safety.

- EPA should continue to collect and use the data needed to evaluate the validity of the threshold assumption, and it should make any needed revisions in the proposed model so that human risks, particularly those of individuals with above-average sensitivity or susceptibility, are accurately estimated.

"Upper-Bound Estimates" versus "Best Estimates"

In a screening-level or semiquantitative risk characterization, component uncertainties associated with predicted cancer risk are not generally aggregated in a rigorous quantitative fashion. In such cases, it is practical to calculate an "upper-bound" point estimate of risk by combining similarly "upper-bound" (and not "best") point estimates of the component quantities involved, particularly for

quantities (such as the dose-scaling factor) that are highly uncertain. For screening-level analyses, the EPA (1992d) proposal to adopt a new interspecies dose-equivalence factor is inconsistent with the 1986 guideline stipulation that risk estimated under the guidelines represents a "plausible upper bound" on increased cancer risk, and it is inconsistent with the corresponding stipulation that "upper-bound" or health-conservative assumptions are to be used at each point in cancer-potency assessment that involves substantial scientific uncertainty.

- For a screening-level or semiquantitative approach in which component uncertainties associated with predicted upper-bound cancer risk are not aggregated in a rigorous quantitative fashion, the EPA guidelines, to determine upper-bound cancer risk, should require the use of an upper-bound (i.e., reasonably health-conservative), rather than a "best," interspecies dose-scaling factor consistent with the best available scientific information.

Uncertainty versus Variability

A distinction between uncertainty (i.e., degree of potential error) and interindividual variability (i.e., population heterogeneity) is generally required if the resulting quantitative risk characterization is to be optimally useful for regulatory purposes, particularly insofar as risk characterizations are treated quantitatively.

- The distinction between uncertainty and individual variability ought to be maintained rigorously at the level of separate risk-assessment components (e.g., ambient concentration, uptake, and potency) as well as at the level of an integrated risk characterization.

Note

1. For example, in the 1980s the Consumer Products Safety Commission (CPSC) had to issue a standard regarding how close together manufacturers had to place the vertical slats in cribs used by infants, with the aim of minimizing the number of accidental strangulations nationwide. Presumably, there was virtually no uncertainty about the diameter of an average infant's head, but there was significant variability in distinguishing different infants from each other. CPSC thus had to make a decision about which estimation of head size to peg the standard to—an "average" estimate, a "reasonable worst case," the smallest (i.e., most conservative) plausible value, etc. We suggest that it is not apropos to use the phrase "better safe than sorry" to apply to this kind of reasoning, because uncertainty is not at work here. Rather, deciding whether to be conservative in the face of variability rests on a policy judgment about how far to extend the attempt to provide safety.

Part III

Implementation of Findings

The committee believes that a major portion of its charge is to consider how its findings and recommendations should be implemented in light of the comprehensive rewriting of Section 112 by Title III of the 1990 amendments to the Clean Air Act. Many of the common problems in health risk assessment might have arisen because of the two most salient features of EPA's implementation of the Red Book paradigm over the last 10 years: the emphasis on single outputs of each step, which are then processed into single numbers for risk; and the separation of the research and analysis functions into discrete, sequential stages.

A tiered system of priority-setting would be an important positive development in the practice of standard-setting and risk analysis. Currently, standards (goals for achieving health and safety) are set in accordance with a Congressional mandate to provide "an adequate margin of safety." Where data do not exist (particularly with respect to responses to low doses and mechanisms of toxicity), EPA has generally chosen default options that, in addition to being in keeping with current scientific knowledge, are intended to be conservative (i.e., health protective) in the outcomes to which they lead. This protective approach provides the basis for developing a stepwise, tiered system for assigning priorities to chemicals to be examined for potential regulation. As a first tier—usually in the absence of data—computations can be made (with the appropriate default assumptions) that lead to a possible regulatory standard. If this standard is readily achievable, no further analysis is called for. If the standard is not achievable, data will be sought to replace the possibly too-conservative default assumptions. Substituting more chemical-specific information for default assumptions will usually lead to less rigid and thus more easily attainable standards (or higher

"safe" doses). (The rare situations in which this relaxation of the standards does not occur would imply that the default assumptions were not sufficiently health protective and so needed to be re-examined.)

A stepwise process that replaces default assumptions with specific data can be expected to yield more and more firmly established standards (regulatory doses); i.e., uncertainty should be reduced as a consequence of having more information. The tiered process for setting standards thus reflects the philosophical process of proceeding from conjecture ("it is reasonable that …") through information to (one hopes) wisdom.

The issue of implementation is discussed in Chapter 12, the final chapter, from two points of view. First, technical guidance is provided on EPA's implementation of the recommendations in a regulatory context. Second, the committee discusses institutional issues in risk assessment and risk management.

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Implementation

Health risk assessment is one element of most environmental decision-making—a component of decisions about whether, how, and to what degree the assessed risk requires reduction. The factors that may be considered by decision-makers depend on the requirements of applicable statutes, precedents established within the responsible government agencies, and good public policy. This chapter discusses how the risk-assessment recommendations in this report could be implemented in the context of Section 112 of the Clean Air Act (as amended in 1990), and it discusses several institutional issues in risk assessment and risk management.

Priority-Setting And Section 112

As we explained in Chapter 2, Section 112 calls for EPA to regulate hazardous air pollutants in two stages. In the first, sources will be required to do what is feasible to reduce emissions. In the second, EPA must set "residual-risk" standards to protect public health with an ample margin of safety if it concludes that implementation of the first stage of standards does not provide such a margin of safety. This second stage will require use of risk assessment.

Neither the resources nor the scientific data exist to perform a full-scale risk assessment on each of the 189 chemicals listed as hazardous air pollutants by Section 112. Nor, as we noted in Part II, is such an assessment needed in many cases.

We therefore urge an iterative approach to risk assessment. Such an approach would start with relatively inexpensive screening techniques and move to

more resource-intensive levels of data-gathering, model construction, and model application as the particular situation warranted. To guard against the possibility of underestimating risk, screening techniques must be constructed so as to err on the side of caution when there is uncertainty. The results of these techniques should be used to set priorities for the gathering of further data and the application of successively more complex techniques. These techniques should then be used to the extent necessary to make a judgment. The result would be a process that supports the risk-management decisions required by the Clean Air Act and that provides incentives for further research, without the need for costly case-by-case evaluations of individual chemicals.

Under an iterative approach, a screening analysis is followed by increases in the refinement of the estimate, as appropriate. In effect, each iteration amounts to a more detailed screen. As we have explained in Chapter 6, screening analyses need to incorporate conservative assumptions to preclude the possibility that a pollutant that poses dangers to health or welfare will not receive full scrutiny.

Considering the effort required to carry out a "full-scale" risk assessment of 189 potentially hazardous substances and the current resources of the agency, it is unlikely that this task can be accomplished within the time permitted by the act if full-scale risk assessments must be conducted by EPA itself. This committee recommends a priority-setting scheme (as described in the following sections) based on initial assessments of each chemical's possible impact on human health and welfare. But Congress should recognize that the resources now available to EPA probably will not support a full-scale risk analysis for each source or even each source category within the time permitted, even with priority-setting. Thus, EPA will need alternatives to full-scale risk assessment, and attention should be given to setting priorities for the allocation of resources. In addition, a full statement of resource requirements should be developed and presented to Congress for its use in decisions about budget and for its understanding and guidance with regard to reducing the task.

Iterative Risk Assessment

To implement Section 112, the committee generally supports the tiered, iterative risk-assessment process proposed by EPA in its draft document as shown in Appendix J. As stated by EPA, this process is based on the concept that as the comprehensiveness of a risk assessment increases, the uncertainty in the assessment decreases.

In the absence of sufficient data or resources to characterize each risk-assessment parameter accurately, EPA deliberately uses default options that are intended to yield health-protective risk estimates. Lower-tier risk assessments that are used for preliminary screening rely heavily on default options, and their results should be health-protective. If a lower-tier risk assessment indicates that an unacceptable health risk could be associated with a particular exposure and a

regulated party believes that the risk has been overestimated, a higher-tier risk assessment can be performed. The higher-tier risk assessment would be based on more precise (and less uncertain) exposure and health information instead of relying on the default options. Conversely, if EPA believes that a lower-tier risk assessment has underestimated the health risk associated with a particular exposure, a higher-tier risk assessment might yield a more reliable estimate.

The following sections evaluate each step in the health-risk assessment process with reference to how EPA plans to implement its tiered approach.

Exposure Assessment

EPA (1992f) has proposed a tiered scheme for using health risk assessments to delist source categories and eliminate residual risk. EPA asserts that this scheme provides health-protective estimates of risk by assuming maximal exposure levels, except for cases related to complex terrains (for which an alternative dispersion model should be selected from the complex-terrain models available to EPA to estimate maximal concentrations of chemicals in air and hence maximal exposure levels).

In the initial step of the tiered approach (see Table 12-1), the emission rate for a facility is multiplied by a dispersion value obtained from a table and chosen on the basis of two site-specific parameters: stack height and the approximate distance to the site boundary line. A generic "worst-case" meteorology applicable to all noncomplex terrain is used to obtain the dispersion factors for a simple Gaussian-plume model with worst-case plant parameters (e. g., zero-buoyancy plume and zero exit velocity).

The second tier uses a simple, single Gaussian-plume model that incorporates site-specific data on the site boundary distance; the stack height, exit velocity, temperature, and diameter; the urban-rural classification; and the building dimensions. Again, a generic worst-case meteorology is used in the calculation.

In the third tier, the modeling would include multiple-point release, local meteorologic characteristics, and the choice of specific local receptor-site locations. The maximal exposure is calculated by multiplying the estimated concentration by residence time. EPA is debating the extent to which it will use less than lifetime residence (i.e., alter the 70-year-lifetime assumption).

In a presentation made to the committee by EPA staff, a fourth tier was described that would incorporate time-activity modeling, as in the Human Exposure Model II (HEM II). HEM-II uses an approach similar to that of the National Ambient Air Quality Standards (NAAQS) Exposure Model (NEM), which has been used in exposure assessments for criteria pollutants (tropospheric ozone, sulfur dioxide, etc.). However, the NEM has not been fully evaluated and validated (NRC, 1991a).

There are a number of difficulties associated with the method in the initial tiers. First, EPA does not specify that a conservative emission rate should be

TABLE 12-1 Summary of EPA's Draft Tiered Risk-Assessment Approach as Presented to the Committee

Tier 1: Lookup Tables

- Two tables: short- and long-term (based on EPA's SCREEN model)
- Inputs: emissions rate, release height, fenceline distance
- Outputs: Maximum offsite concentration (focus on maximum exposed individual, MEI) Maximum offsite cancer risk (based on unit risk estimate, URE) Chronic noncancer hazard index (based on chronic health thresholds) Acute noncancer hazard index (based on acute health thresholds)

Tier 2: Screening Dispersion

- Based on EPA's SCREEN model (uses conversion factor for long-term)
- Inputs: Tier 1 + stack diameter, exit velocity and temperature, rural/urban classification, and building dimensions
- Outputs: Maximum offiste concentration and downwind distance (focus on MEI) Cancer risk and/or noncancer hazard index

Tier 3: Site-Specific Dispersion Model

- Based on EPA's TOXLT, TOXST models (uses the ISC dispersion model)
- Inputs: Tier 1 + Tier 2 + local meteorology, release point and fenceline layout, terrain features, release frequency, and duration
- Outputs: Long-term - receptor-specific risk, chronic noncancer hazard index (MEI) Short-term - receptor-specific hazard index exceedance rate (MEI)
- Ambient monitoring used to enhance modeling or as alternative on case-by-case basis for difficult modeling applications

Tier 4: Site-Specific Dispersion and Exposure Model

- Based on EPA's HEM II model
- Inputs: Tier 3 + population model
- Outputs: Maximum offsite concentration (MEI), exposure distribution, and population risk (incidence) with optional characterization of uncertainties
- Personal monitoring used as alterative on case-by-case basis for difficult modeling applications

NOTES:
(1) Approach considers flat or rolling terrain only;
(2) Complex terrain alternatives used on case-by-case basis;
(3) Analysis considers only direct inhalation exposure;
(4) Tiers proceed from most conservative and least data intensive (Tier 1) to least conservative and most data intensive (Tier 4).
SOURCE: Guinnup, 1992 (see Appendix J).

used; it will use the emission rate for normal operation of a plant at full capacity. In addition, none of EPA's current emission estimation methods accounts for "upset" situations with higher than normal emissions or for the emission-estimate uncertainty. Therefore, current emission estimates cannot be relied on as necessarily conservative.

Second, the committee reiterates its earlier concern (see Chapter 7) about the use of the Gaussian-plume model beyond the lower-tier screening level. Even there, complex terrain can create substantial problems. The EPA complex terrain models have focused on emissions released from tall stacks toward the side of a hill or valley, and not on poor dispersion of material from a point or area source within a valley. Models for complex terrain have been developed and evaluated by the atmospheric-research community. The committee does not recommend any specific model, but suggests that EPA look beyond its set of existing models to find the best possible ones for the dispersion of hazardous air pollutants in the particular type of complex terrain that applies in each case. In addition, models should be considered that account for the possibility of a negative buoyancy plume (i.e., gas heavier than air).

For the conditions under which hazardous air pollutants are emitted from many emission points within a plant, EPA has not demonstrated that the simple, single Gaussian-plume approach (choosing dispersion values from a table generated on the basis of a generic worst-case meteorology and worst-case plant-dispersion characteristics) will be appropriate for all the situations to which it might be applied. The Gaussian-plume models have been tested for the dispersion of criteria pollutants from point sources that typically have good dispersive characteristics (e.g., tall stacks, high thermal buoyancy, and high exit velocity). However, it has not been demonstrated that this generic worst-case meteorology is fully representative of any location, such as cities with substantial local perturbations in the dispersion characteristics (surface roughness, street canyon, heat island effects, etc.). The committee recommends that, until the evaluations can be completed, exposure assessment for source delisting and evaluating residual risk begin at EPA's current Tier 3, where the industrial source complex (ISC) model with local meteorology and local receptor-site choices will provide better estimates of the worst-case possibilities. If Tiers 1 and 2 can be shown definitively to estimate exposure conservatively, they could be incorporated into the delisting, priority-setting, and residual-risk process.

In accordance with the discussion in Chapter 7, the committee recommends that distributions of pollutant concentration values be estimated with available evaluated stochastic dispersion models that provide more realistic descriptions of the atmospheric dispersion process and that incorporate variability and uncertainty in their estimates. If the screening process suggests that a source cannot be excluded from further review, exposure estimation should be more comprehensive and incorporate more advanced methods of emission characterization, stochastic modeling of dispersion, and time-activity patterns, as discussed in

Chapter 7. Exposure assessment can be improved as necessary by incorporating more explicit local topographic, meteorologic, and other site-specific characteristics. However, if the regulated sources find it acceptable to be regulated on the basis of a (truly conservative) screening analysis, then there should be no obligation to go further. If they are not content, then the sources should bear the burden of doing the higher-tier analysis, subject to EPA guidelines and review.

Assessment of Toxicity

In EPA's proposed approach, four metrics will be used to determine whether the predicted impact of a source should warrant concern: lifetime cancer risk, chronic noncancer hazard index, acute noncancer hazard index, and frequency with which acute hazard index is exceeded. The toxicity data needed to evaluate these metrics, such as weight-of-evidence characterizations and cancer potencies for carcinogenicity and reference concentrations (RfCs) for noncancer end points, can be found by referring to the Integrated Risk Information System (IRIS) online database (Appendix K). This database is maintained by EPA's Environmental Criteria and Assessment Office within the Office of Research and Development for use by EPA's various program offices, by state air-quality and health agencies, and by other parties that look to EPA to provide current information on chemical toxicity.

The IRIS database will be the primary source of toxicity data for the tiered risk-assessment approach described here. The committee believes that it is appropriate for EPA to use IRIS as its preferred data source for toxicity information, rather than duplicate the effort needed to assemble and maintain such information for those of the 189 chemicals specified in Section 112 that are in IRIS. For chemicals that require a higher-tier risk assessment, EPA could supplement the information in IRIS with additional data, probability distributions, and modeling approaches. For Section 112 chemicals not yet in IRIS, EPA must collect and enter data on carcinogenic and noncarcinogenic effects.

For many of the 189 chemicals now on the Section 112 list, there are no IRIS entries, or the existing entries do not include cancer potencies for suspected carcinogens or RfCs for chemicals suspected of causing acute or chronic noncarcinogenic health effects. In these cases, it will be appropriate for EPA to develop crude screening estimates of cancer potencies and RfCs for use in research planning; if the screening values are entered in IRIS, they should be clearly identified as screening values. These estimates should be combined with exposure estimates to calculate potential cancer risks and the likelihood of acute and chronic noncancer health effects. Such estimates may be based, for example, on in vitro tests for carcinogenicity, expert judgment on structure-activity relationships, and other available information and judgment on the toxicity of the chemical in question. These crude estimates should not be used as a basis for regulatory decisions when the supporting data are not adequate for such use. However,

an entry can and should summarize current information on the extent to which a chemical might be a potentially important threat to public health. If a bioassay of the chemical is under way through the National Toxicology Program or elsewhere, the estimated date of availability of results should be stated in IRIS.

A review of IRIS by the EPA Science Advisory Board (SAB) noted the importance of IRIS for both EPA and non-EPA users (Appendix K). If IRIS entries are to be used for risk assessments that lead to major risk-management decisions, then EPA must ensure their quality and keep them up to date. It is EPA's standard practice that IRIS files must be assessed in their entirety so that cancer potencies and RfCs are not distributed without an accompanying narrative description of their scientific basis; IRIS is intended not only as a source of numerical data, but also as an important source of qualitative risk-assessment information. The appropriate caveats and explanations of numerical values are important for keeping risk managers and other IRIS users fully informed about health-risk information.

The SAB noted that chemical-specific risk assessments, such as Health Assessment Documents (HADs) and SAB reviews of HADs, should be referenced and summarized in IRIS. Where different risk assessments have yielded different cancer potencies or RfCs, the file should include an explanation that relates these differences to variations in data, assumptions, or modeling approaches. Data deficiencies and weaknesses in a risk assessment that might be remedied through further data collection and research should be described in the file. In this way, IRIS can evolve into a high-quality information support system for the needs of EPA and other users relative to the Section 112 chemicals, providing not just one set of numbers for dose-response assessment, but also a summary of alternative approaches, their strengths and weaknesses, and opportunities for further research that could improve risk estimates.

Summary

The committee supports EPA's general concept of tiered risk assessment with two modifications. First, the tiered approach requires a conservative first level of analysis. EPA asserts that its approach provides a conservative risk estimate, except in the case of complex terrain. But EPA has not yet demonstrated that this assertion is valid. Second, rather than stopping a risk assessment at a particular point, EPA should encourage and support an iterative risk-assessment process wherein improvements in the accuracy of the risk estimate will replace the initial screening estimate. This process will continue until one of three possible conclusions is reached: (1) the risk, assessed conservatively, is found to be lower than the applicable decision level (e.g., 1 in a million excess lifetime risk of cancer); (2) further improvements in the model or data would not significantly change the risk estimate; or (3) the source or source category determines that the cost of reducing emissions of this pollutant are not high enough for it to

justify the investment in research required for further improvements in the accuracy and precision of analysis. This procedure provides private parties with the opportunity to improve the models and data used in the analysis.

EPA must avoid interminable analysis. At some point, the risk-assessment portion of a decision should end, and a decision should be made. Reasonable limits on time (consistent with statutory time limits) and resources must be set for this effort, and they should be based on a combination of the regulatory constraints and the benefits gained from additional scientific analysis. It is not necessary to determine or measure every variable to high accuracy in the risk-assessment process. Rather, the uncertainties that have the most influence on a risk assessment should be the ones that the risk assessor most seeks to quantify and then reduce.

Epa Practices: Points To Consider

The committee throughout this report has noted differences between the methods EPA is currently using and practices the committee considers useful in the risk-assessment process. The committee's recommendations (summarized below) highlight differences that should be considered in the process of EPA's undertaking its proposed tiered risk assessment approach.

- Select and validate an appropriate emission and exposure-assessment model for each given implementation in the risk-assessment process.
- Use a carcinogen-classification scheme that reflects the strength and relevance of evidence as a supplement to the proposed narrative description.
- Screen the 189 chemicals for programmatic priorities for the assessment of health risks, identify gaps in the data on the 189 chemicals, develop incentives to expedite generation of the needed data, and evaluate the quality of data before their use.
- Clarify defaults and the rationales for them, including defaults now "hidden," and develop criteria for selecting and departing from the defaults.
- Clarify the sources and magnitudes of uncertainties in risk assessment.
- Develop a default factor or procedure to account for the differences in susceptibility among humans.
- Use a specific conservative mathematical estimation technique to determine exposure variability.
- Conduct pediatric risk assessments whenever children might be at greater risk than adults.
- Evaluate all routes of exposure to address multimedia issues.
- Use an upper-bound interspecies dose-scaling factor for screening-level estimates.
- Fully communicate to the public each risk estimate, the uncertainty in the risk estimates, and the degree of protection.

Implications for Priority-Setting for Title III Activities

With a large number of hazardous air pollutants, hundreds of source categories, and perhaps hundreds of sources within many of those categories, and with strains on personnel and financial resources. EPA will need to set priorities on its actions under Section 112. In addition, Title IX of the Amendments requires EPA to perform health assessments at a rate sufficient to make them available when needed for the residual risk assessments under Title III (approximately 15 per year). To respond to these requirements, EPA will have to determine data needs, the level of analysis needed, and the criteria for determining priorities under the Clean Air Act, as well as seek sufficient funds for conducting these analyses.

It is important that EPA establish priorities for its risk assessment activities. In the past, EPA has often appeared to base its priorities on the ease of obtaining data on a particular chemical. Rather, EPA should acknowledge the relevance and strength of the existing data on each of the 189 chemicals (and mixtures) on the list, identify the gaps in scientific knowledge, and set priorities for filling the gaps so that research that is likely to contribute the most relevant information in the most time- and cost-effective manner will be conducted first.

At a minimum, an inventory of the relevant chemical, toxicologic, clinical, and epidemiologic literature should be compiled for each of the 189 chemicals (or mixtures). For each chemical without animal test data, a structure-activity evaluation should be conducted; and for each mixture, results of available short-term toxicity tests should be analyzed. If the evidence from this step or from reviews of the clinical, epidemiologic, or toxicologic literature suggests potential human health concerns, aggregate emission data and estimates of potentially exposed populations should be reviewed. The completed preliminary analyses, including a description of the assessment process used and the findings, should be placed in the public domain (e.g., IRIS or another mechanism readily accessible to the public). The inclusion of exposure data would represent a departure from past practices, and the database might need to be restructured to accommodate this new information.

For any chemical (or mixture) for which preliminary results suggest a potential health concern, it is appropriate to use more accurate emission data (including existing source-specific data), information on the environmental fate and transport of the chemical (or mixture), and more accurate characterizations (e.g., types and estimated numbers) of the populations that may be at risk of exposure, including potentially sensitive subpopulations such as children and pregnant women. In addition, a more intensive review of the relevance and strength of the available animal and human evidence (including toxicologic, clinical, and epidemiologic) data should be developed to refine insights into the probable human-health end points. If the evidence on a chemical (or mixture) and exposure still suggests potential human health effects, the agency should conduct a comprehensive

risk assessment. This assessment should be conducted and communicated in accord with the recommendations elsewhere in this report, and the limitations of the data and the related assumptions, limitations, uncertainties, and variability should be appropriately stated with the final output of the assessment.

In summary, this iterative approach to gathering and evaluating the existing evidence is intended to produce a risk assessment for each of the 189 chemicals (or mixtures) that is appropriate to the quality and quantity of available evidence, the estimated size of the problem, and the most realistic scientific judgment of potential human-health risks based on that evidence. The committee believes that the process will result in a time- and cost-efficient mechanism that will effectively set priorities among the 189 chemicals (or mixtures) that fit the probable public-health concerns about them.

Model Evaluation and Data Quality

Data should not be used unless they are explicitly judged to be of sufficiently high quality for use in an activity as sensitive as risk analysis. No data should be incorporated into the risk-assessment process unless the method used to generate them has been peer-reviewed before its use. Table 12-2 indicates some steps that EPA could take to substantiate and validate its models and assumptions before use.

EPA should take additional steps to ensure that methods used to generate data for risk assessments are scientifically valid, perhaps through the use of its Science Advisory Board or other advisory mechanisms. A process for public review and comment, with a requirement for EPA to respond, should be available so that industry, environmental groups, or the general public may raise questions regarding the scientific basis of a decision made by EPA on the basis of its risk-assessment process.

Default Options

We have noted in previous chapters that EPA should articulate more explicit criteria by which it will decide whether it is appropriate to use an alternative to a default in risk assessment. Such criteria may be expressed either in the form of a general standard or in terms of specific types of evidence that the agency considers acceptable.

Critics of EPA's use of defaults have characterized the issue of their scientific validity in binary terms: either they are supported by science, in which case they are deemed legitimate, or they are contradicted by new knowledge, in which case they might be too conservative or not sufficiently protective. The reality that EPA confronts is more complex than that dichotomy. New scientific knowledge is rarely conclusive at its first appearance and rarely gains acceptance overnight. Rather, evidence accumulates, and its validity and weight are gradually

TABLE 12-2 Example of Procedure for Methods, Data, and Model Evaluation

Database Evaluation and Validation
1. Develop data-quality guidelines that require all data submitted to agency to meet minimal quality level relative to their intended use before use in given risk-assessment tier.
2. Conduct critical review of data-gathering and data-management systems to ensure that quality and quantity of data are sufficient to meet EPA's risk-assessment responsibilities under act.
3. Document procedures used to develop data, including why particular analytic or measurement method was chosen and its limitations (e.g., sources of error, precision, accuracy, and detection limits).
4. Characterize and document data quality by indicating overall robustness, spatial and temporal representativeness, and degree of quality control implemented; define and display accuracy and precision of measurements; indicate how missing information is treated; identify outliers in data.
5. Account for uncertainty and variability in collection and analysis of data.
Model Evaluation and Validation
1. Develop model-validation guidelines that indicate minimal quality of model that can be used for given risk-assessment purpose.
2. Conduct critical review of each model used in risk-assessment process to ensure that quality and quantity of output of each model are sufficient to meet EPA's risk-assessment responsibilities under act.
3. Assess database and establish and document its appropriateness for model selected.
4. Conduct sensitivity testing to identify important input-controlling parameters.
5. Assess accuracy and predictive power of model.

established through a transition period. The challenge for EPA is to decide when in the course of this evolutionary development the evidence has become strong enough to justify overriding or supplementing an existing default assumption.

Management considerations can appropriately be permitted to influence science-policy decisions related to deviations from established default positions. The committee emphasizes the desirability of well-articulated criteria for deviation from defaults. If new scientific evidence suggest that a supposedly conservative default option is not as conservative as previously believed, a new default option might be substituted. EPA needs a procedural mechanism that will allow departure from existing default models and assumptions. A more formal process should be developed.

Uncertainty Analysis

Not characterizing the uncertainty in an analysis can lead to inappropriate decisions. In addition, attempting to incorporate default assumptions of unknown conservatism into each step of a risk assessment can lead to an insufficiently or too conservative analysis.

The committee believes that the uncertainty on a risk (i.e., risk characterization) can be handled in three ways:

1. Conduct a conservative screening analysis.
2. Conduct a generic uncertainty analysis.
3. Conduct testing or analysis to develop plant-specific and chemical-specific probability distributions.

A possible uncertainty-analysis process is described in Table 12-3. As stated earlier, a key factor in deciding to increase the scope and depth of uncertainty analysis should be the extent to which expected costs and risks might alter decisions.

For parameter uncertainty, enough objective probability data are available in some cases to permit estimation of the probability distribution. In other cases, subjective probabilities might be needed. For example, a committee might conclude on the basis of engineering judgment that emission estimates calculated with emission factors are likely to be correct to within a factor of 100 (see discussion in Chapter 7) and be approximately lognormally distributed. Thus, the median of the estimated distribution would be set equal to the observed or modeled emission estimate, and the geometric standard deviation would be taken as approximately 10. If making such a generic-uncertainty assumption and then picking a conservative estimator from the distribution leads to an estimate that is above the relevant decision-making threshold, that should govern the decision unless affected parties wish to devote more resources to improving the risk characterization. If the risk characterization is sufficient for decision-making purposes, then it will not be necessary to improve it.

Institutional Issues In Risk Assessment And Management

EPA's conduct of risk assessment has been evaluated in previous chapters largely from a technical perspective, with the aim of increasing the scientific reliability and credibility of the process. But EPA operates in a decision-making context that imposes pressures on the conduct of risk assessment, and these contextual pressures have led to recurrent problems of scientific credibility, the most important of which were noted in Chapter 2.

Criticisms of EPA's risk assessments take a variety of forms, but many of them focus on three basic decision-making structural and functional problems: unjustified conservatism, often manifested as unwillingness to accept new data or abandon default options; undue reliance on point estimates generated by risk assessment; and a lack of conservatism due to failure to accommodate such issues as synergism, human variability, unusual exposure conditions, and ad hoc departures from established procedures. Although some of those criticisms might have been overstated (and we provide evidence in earlier chapters that they

TABLE 12-3 Example of Procedure for Uncertainty Analysis

Preliminary Steps

1. Conduct generic review of each parameter in each step of risk-assessment process and determine default distribution on the basis of objective probabilities, if possible, or subjective probabilities, if sufficient information is not available. If subjective probabilities cannot be used because of lack of consensus, assume either continuous-uniform or discontinuous-dichotomous distribution between reasonable lower and upper bounds or if unimodality is reasonable assumption, triangular distribution (between reasonable upper and lower bounds) or lognormal distribution (with reasonable estimates of geometric mean and standard deviation).

Improving Generic Uncertainty Analysis

2. If it is decided that default uncertainty analysis should be improved, conduct review of default probability distribution for each parameter to determine whether default distribution is reasonable. If this distribution is *not* reasonable, conduct step 3 by either of two methods:.

3a. Conduct sensitivity analysis by replacing each component distribution with its corresponding mean.	3a. Conduct sensitivity analysis by identifying most influential parameters for each model component (sensitivity index = change in model result per unit change in value of parameter)
3b. Select probability distribution for most-sensitive parameters on basis of experience, judgment, and available information from existing data samples, parameter-value ranges, most likely values, or range of most likely values.	3b. Determine uncertainty in each parameter—e.g., uncertainty index = ratio of standard deviation of parameter × to mean value of parameter ×, or number of orders of magnitude of uncertainty = log(ratio of upper-bound order statistic corresponding lower-bound order statistic).
	3c. Determine model sensitivity-uncertainty index by multiplying sensitivity index for each parameter by its uncertainty index.
	3d. Select probability distribution for *only* influential parameters on basis of experience, judgment, and available information from existing data samples, parameter-value ranges, most likely values, or range of most likely values.

Uncertainty Analysis Flowchart

4. Conduct a Monte Carlo analysis by using probability distributions of parameters as input for simplified versions of each model (e.g., emissions, exposure, and dose-response relationship) to generate a set of synthetic (Monte Carlo) probability distributions for output from each model. Approaches other than Monte Carlo might be equally feasible.

Uncertainty Analysis Flowchart—*continued*

5. For each plausible scientific model (i.e., the default plus any plausible alternatives), conduct a numerical analysis (e.g., Monte Carlo) to determine the probability-distribution function of risk due to uncertainty in the parameters selected in Step 4. Present each distribution separately or combine them into a single representation, clearly indicating which portions of the distribution are derived from fundamental controversy about which model might be correct.
6. Conduct a "reality check" to ensure that resulting risk-estimate distribution makes scientific sense; if not, adjustments may be made. Objective of this analysis is to improve representation of uncertainty. Clearly state that uncertainty representation does not characterize all uncertainty associated with estimated risk.
7. Repeat analysis for each type of risk measurement (e.g., individual risk, population risk, and years of life lost) needed for decision-making.

Risk Management

8. Judge what probability provides sufficient level of confidence relative to regulatory decision needed. For example, risk manager might judge mean of upper 5% of distribution to be point estimate that is appropriately "conservative" within context of regulatory decision. This is simple way to guarantee modest but tangible amount of conservatism with respect to *both* average and upper tail of uncertainty distribution.

might have been), it is important for EPA to understand the features of its internal organization, decision-making practices, and interactions with other federal agencies that lead to these criticisms of its performance. The agency's prevailing assumptions concerning the appropriate role of risk assessment and its relationship to risk management also should be re-examined.

Stability and Change

Like any other complex organization, EPA is subject to many competing institutional pressures that affect the quality and credibility of its decisions. The agency is expected to use the best possible science in risk assessment; yet assessments must often be carried out under conditions that preclude deliberation or continued study. Problems of intra-agency coordination that have persisted throughout EPA's history create communication gaps between risk assessors and managers. The firefighting mode in which the agency all to often operates hinders the design of effective long-range research programs and even the formulation of the right questions for science to answer. As in all bureaucracies, it often seems safest to take refuge in established approaches, even if these have begun to appear scientifically outdated. External pressures, such as the demands of state agencies for precise guidance, strengthen this tendency.

These overarching managerial problems are faced by any regulatory body that is responsible for rendering consistent decisions based on changing scientific

knowledge. Uncertainty, variability, and imperfections in knowledge make it difficult to control environmental risks. To remain accountable to the public under these circumstances, regulatory agencies like EPA must assess uncertain science in accordance with principles that are fully and openly articulated and applied in a predictable and consistent manner from case to case. Risk-assessment guidelines and default assumptions were designed to accomplish those objectives, and they have succeeded to a large extent in making EPA's both transparent and predictable.

But an unintended side effect of such explicit decision-making rules is that they can run the risk of becoming rigid over time to the detriment of scientific credibility. Science-policy rules might ensure a valuable degree of consistency from one case to another, but they do so in part by sometimes failing to stay abreast of changing consensus in the scientific community. Some have criticized EPA for allowing bureaucratic considerations of consistency to override good scientific judgment. In trying to ensure that like cases are treated alike, the agency might fail to acknowledge, or even recognize, the scientific reasons why a new case is substantially unlike others in ostensibly the same category. In short, risk-assessment guidelines can be applied in practice like unchangeable rules. That is unfortunate, as articulated earlier in the discussion on guidelines versus requirements.

Since the mid-1970s, numerous reports and proposals have addressed the generic problem of enlisting the best possible science for EPA's decision-making. We note, for example, a January 1992 report, *Safeguarding the Future* (EPA, 1992f), submitted to the EPA administrator and containing detailed recommendations for strengthening EPA's scientific capabilities. Such reports have stressed the need for high-quality scientific advice, expanded peer review, and adequate incentives for staff scientists—clearly important issues that have attracted attention at the highest levels of EPA's administration, but have not been effectively implemented. The agency's decision-making practices have evolved since the mid-1970s, defining a positive, although gradual, learning curve. There can be little doubt that EPA is aware, at a conceptual level, of steps that can be taken to improve both its in-house scientific capabilities and its collaboration with the independent scientific community.

Management As Guide To Assessment

A more subtle and less widely recognized impediment to good decision-making on risk arises from a rigid adherence to the principle of separating risk assessment from risk management. The call to keep these two functions distinct was originally articulated in response to a widespread perception that EPA was making judgments on the risk posed by a particular substance not on the basis of science, but rather on the basis of its willingness to regulate the substance. The purpose of separation, however, was not to prevent any exercise of policy judgment

at all when evaluating science or to prevent risk managers from influencing the type of information that assessors would collect, analyze, or present. Indeed, the Red Book made it clear that judgment (also referred to as risk-assessment policy or science policy) would be required even during the phase of risk assessment. The present committee concludes further that the science-policy judgments that EPA makes in the course of risk assessment would be improved if they were more clearly informed by the agency's priorities and goals in risk management. Protecting the integrity of the risk assessment, while building more productive linkages to make risk assessment more accurate and relevant to risk management, will be essential as the agency proceeds to regulate the residual risks of hazardous air pollutants.

Risk assessment should be an adjunct to the Clean Air Act's primary goal of safeguarding public health, not an end in itself. A legitimate desire for accuracy and objectivity in representing risk can induce such an obsession with numbers that too much energy is expended on representing the results of risk assessment in precise numerical form. Thus, new research might be commissioned because there is insufficient notice of how marginal the results would be in a given case or without consideration of new, less resource-intensive methods of providing essential inputs.

Moreover, there might be a vast difference between having "the truth" and having enough information to enable a risk manager to choose the best course of action from the options available. The latter criterion is more applicable in a world with resource and time constraints. Determining whether "enough information" exists to decide in turn implies the need to evaluate a full range of decisions. Thus, further improvement of a risk-assessment estimate might or might not be the most desirable course in a given situation, especially if the refinement is not likely to change the decision or if disproportionate resources have been directed to studying the risk at the expense of creating a full set of decision options from which to choose.

Comparisons of Risk

It can be questioned whether risk assessment is sufficiently developed for the particular class of decisions regarding "offsets" or other tradable actions. In general, because of the substantial and varied degrees of model and parameter uncertainties in risk estimates, it is almost impossible to rank relative risks accurately unless the uncertainty in each risk is quantified or otherwise accounted for in the comparison. If the regulatory need for comparison of risks is imperative, one might attempt to compute the uncertainty distribution of the ratio of the two risks and choose from it one or more appropriate summary statistics. For example, one might determine in a given case that there is a 90% chance that chemical A is riskier than chemical B and a 50% chance that it is at least 10 times as risky. Also, if EPA decides to undertake the proposed iterative approach to risk assessment

it will not be possible to apply this kind of ratio comparison to estimates derived from different tiers of analysis. That is because the analyses at each level will be conducted differently and will produce risk estimates of differing accuracy and conservatism. The same might be true of aggregation of risks associated with different exposures.

Even more difficult is the issue of the relative degrees of reliability in the risk figures being compared. Is it appropriate, for example, to compare actuarial risks with modeled risks? Those and other difficulties suggest that EPA should pay more attention that it now does to the appropriateness of various procedures for risk comparison. A scientifically sound way to do this would be to modify risk-assessment procedures to characterize more specifically the uncertainties in each comparison of risks—some larger, some smaller than the uncertainties in individual risk assessments—and this could be done across tiers.

Risk Management and Research

Improved cooperation between EPA's Office of Air Quality Planning and Standards (OAQPS), which conducts the regulatory work of the air program, and its Office of Research and Development (ORD), which conducts research and revises the risk-assessment guidelines, would be helpful in ensuring that research needs of the risk-management side were met by the research side. For example, the two groups might jointly publish a research agenda on hazardous air pollutants, submit the agenda for public comment and SAB review, publish a final agenda based on these comments, and then report annually on how much progress has been made on the agenda. EPA should have a review and research-management system that catalogs risk-assessment weaknesses as identified by the SAB and other peer-review activities and that helps to direct research within EPA (and to guide strategies in other federal and state agencies and in the private sector) to remedy the weaknesses when the importance of a risk assessment justifies the expenditure of research funds. In many cases, the regulated parties may be willing to fund research that will enable health-protective default options in risk assessment to be replaced by more complex and less conservative alternatives. EPA will need to maintain its own substantial research capability to understand and evaluate advances in risk assessment. In some cases, EPA will want to support targeted risk-assessment research and data collection on specific chemicals that could lead to revisions in risk assessments of such chemicals. Situations might be discovered where current risk-assessment practice is underestimating health risk or where the information base for a chemical is not sufficient to allow regulation to proceed.

Present EPA practice is to remove IRIS listings while cancer potencies or RfCs are under review. This practice is frustrating to non-EPA users, not only because the information becomes inaccessible, but also because EPA has been reluctant to state when such information will be returned to the system. The

committee believes that a better practice would be for EPA to retain listings in the database, inform users that it is conducting a review, and perhaps include alternatives that can be used in the interim as the basis for calculated cancer potencies and RfCs. The narrative supporting the information on each chemical in IRIS should inform users about the assumptions underlying each calculation, about sources of data and judgments about uncertainty and variability, and about research under way to improve risk assessment on the chemical in support of future regulatory decisions.

Risk Assessment as a Policy Guide

Allocations of public-health resources reflect, among other things, some estimate of the potential benefits from health improvements achieved, and risk assessment is an important tool for understanding potential public-health impacts. Seen from this perspective, risk assessment should be a principal component of public-health and regulatory programs. Risk-management approaches will differ, perhaps greatly, depending on political choices. But establishing the relative impacts of various resource-allocation for achieving risk reduction, by continuing pursuit of comprehensive assessments of risks, should always be an objective.

For example, the committee is concerned that neither Section 112 nor other legislation provides for appropriate control of toxic emissions from mobile and indoor sources. There is strong evidence that public exposure to chemicals (and radiation) in these settings can give rise to higher public-health risk in many cases than outdoor exposure due to stationary-source emissions.

Focusing regulation on the source, rather than on the overall reduction of the pollutant (and its potential risk to public health), is unlikely to be very cost-effective in reducing disease, although it might effectively reduce high individual risks and reduce public concern over involuntary exposures. Given limited funds for both the analysis and control of environmental problems, some believe that EPA should focus on environmental toxicants that pose the greatest publichealth threat.

Social and Cultural Factors

Although the principle of maximal risk reduction is of central importance, some social and cultural factors that might introduce different risk-management priorities also need to be considered.

First, it is apparent from many studies that people's perceptions of relative risk do not always match those of technical experts. When it comes to comparing risks, most people evaluate not only the mathematical probability than an adverse outcome will occur—the principal concern of the technical expert—but also other less tangible features of the risk context, most of which are not generally

considered by the risk assessor. These other concerns should be expressed and reflected at the stage of risk management.

For example, people generally feel greater anxiety about relatively low probability events with catastrophic outcomes (such as an airplane crash) than about higher-probability activities that take only a few lives at a time (such as an automobile collision). People are reluctant to accept risks, no matter how small, unless they feel that the risky activity or exposure provides some personal benefit. Risks believed to be imposed by others are less well tolerated than those voluntarily assumed. In a related vein, risks perceived as being of natural origin are less threatening than risks created by other human beings. Risks that scientists do not understand well, and over which they publicly disagree, are more feared than those about which scientific consensus is strong. Buttressing these observations is additional research that helps us to understand why people, and their governments, seem at times much more anxious about, and willing to act against, the risks associated with industrial chemicals than risks that scientists believe are more important from a public-health perspective (Slovic, 1987), We know, for example, that public perceptions of the need for regulation are influenced by such concerns as people's trust in government, their experience with experts' reassurances, and their views about social justice. When public opinion appears to be exaggerating the risks associated with industrial products, their fear might in fact be founded on an understandable mistrust of the institutional context in which those risks are produced, assessed, and eventually controlled.

Summary

Apart from its specific findings and recommendations, the committee's report is dominated by a number of central themes:

1. EPA should retain its conservative, default-based approach to risk assessment for the purposes of screening analysis for standard-setting; however, a number of corrective actions are necessary for this approach to work properly.
2. EPA should rely more on scientific judgment and less on rigid procedures by taking an iterative approach to its work. Such judgment demands more understanding of the relationship between risk assessment and risk management and a creative but disciplined blending of the two.
3. The iterative approach proposed by the committee provides the ability to make improvements in both the models and data used in its analysis. However, in order for this approach to work properly, EPA needs to provide justification for its current defaults and set up a procedure such as that proposed in the report that permits departures from the default options.
4. When reporting estimates of risk to decision-makers and the public, EPA should report not only point estimates of risk but also the sources and magnitudes of uncertainty associated with these estimates.

Findings And Recommendations

General findings and recommendations regarding implementation and risk management are presented below.

Tiered vs. Iterative Risk Assessment

EPA proposes to adopt a tiered risk-assessment approach that will begin with a "lookup" table and move to deeper analysis with the amount of conservatism generally decreasing as estimated uncertainty decreases.

- Rather than a tiered risk-assessment process, EPA should develop the ability to conduct iterative risk assessments, allowing improvements in the process until the risk, assessed conservatively, is below the applicable decision-making level (e.g., 1×10^{-6}, etc.); until further improvements would not significantly change the risk estimate; or until EPA, the source, or the public determines that the stakes are not high enough to warrant further analysis.

Verification of Amount of Risk-Assessment Conservatism

In its tiered approach, EPA plans to use exposure models developed and validated for criteria pollutants, but not fully evaluated for the broader group of situations including hazardous air pollutants. In particular, it has not shown that analysis conducted with a simple, single Gaussian-plume approach with the generic worst-case conditions will necessarily be conservative over all situations in which it would be applied.

- Until the accuracy and conservatism of the proposed models can be evaluated, EPA should consider beginning at Tier 3, where site-specific data will provide better estimates needed for such key decisions as delisting, priority-setting, and residual-risk decisions.

Full Set of Exposure Models

Even at Tier 3, EPA plans to use a Gaussian-plume model that does not hold over complex terrain. EPA's complex-terrain models focus on tall stacks, rather than the effects of hills or valleys, and emissions from a low point or area source disperse poorly in these models.

- The committee recommends no specific model, but EPA should look beyond the set of models it now uses to find the best possible models of dispersion of hazardous air pollutants in complex terrain.

IRIS Data Quality

EPA plans to use IRIS as the database for as many as possible of the 189 Section 112 chemicals. The IRIS database has quality problems and is not fully referenced.

- EPA should enhance and expand the references in the data files on each chemical and include information on risk-assessment weaknesses for each chemical and the research needed to remedy such weaknesses. In addition, EPA should expand its efforts to ensure that IRIS maintains a high level of data quality. The chemical-specific files in IRIS should include references and brief summaries of EPA health-assessment documents and other major risk assessments of the chemicals carried out by the agency, reviews of these risk assessments by the EPA Science Advisory Board, and the agency's responses to the SAB reviews. Important risk assessments carried out by other government agencies or private parties should also be referenced and summarized.

Toxicity Data Development

Some of the 189 chemicals lack cancer potencies or RfCs.

- If IRIS does not contain a cancer potency or RfC, EPA should develop a procedure for making crude screening estimates. These estimates should generally not be used for regulation, but only as a means of setting research priorities for carrying out the animal studies from which cancer potencies and RfCs could be calculated with EPA standard default methods. EPA should develop a summary of health-risk research needs from a review of the IRIS files on the 189 chemicals. EPA should determine which research is most important, how much of it is likely to be carried out by other parties, and what research should be carried out by EPA and other federal agencies under their mandates to protect public health.

Full Data Set for Priority-Setting

EPA often appears to base priorities on the simple availability of data on a particular chemical.

- At a minimum, EPA should compile for each of the 189 chemicals an inventory of the existing and relevant chemical, toxicologic, clinical, and epidemiologic literature. For each specific chemical, EPA should have at a minimum a structure-activity evaluation; and for each important mixture, it should complete an analysis of available short-term toxicity tests (such as the Ames test). If review of toxicity information suggests a possible need for regulation to protect human health, it should develop aggregate emission data and estimates of populations potentially exposed.

Iterative Priority-Setting

EPA sometimes appears to base its priorities on a one-time analysis of incomplete and preliminary data.

- EPA should take an iterative approach to gathering and evaluating existing evidence to use in a level of risk assessment for each of the 189 chemicals that is appropriate for the quality and quantity of available evidence and the most realistic scientific judgment of potential human health risks. On the basis of that evidence, EPA should further maintain a continuing oversight of new scientific results so that it can identify needs to re-examine chemicals that it has already assessed.

Full and Complete Documentation of Priority-Setting

EPA does not always clearly communicate the methods and data on which it bases its priority-setting analysis. In addition, emission, exposure, and toxicity information is not often collected in the same database.

- Once EPA's preliminary priority-setting analyses are completed for a chemical on the list, a description of the assessment process used, the findings, and the emission, exposure, and toxicity information should be placed in one location in the public domain (e.g., in IRIS).

Guidelines vs. Requirements

EPA and others often interpret the term *risk assessment* as a specific methodologic approach to extrapolating from sets of human and animal carcinogenicity data, often obtained in intense exposures, to quantitative estimates of carcinogenic risk associated with the (typically) much lower exposures experienced by human populations.

- EPA should recognize that the conduct of risk assessment does not require any specific methodologic approach and that it is best seen not as a number or even a document, but as a way to organize knowledge regarding potentially hazardous activities or substances and to facilitate the systematic analysis of the risks that those activities or substances might pose under specified conditions. The limitations of risk assessment thus broadly conceived will be clearly seen as resulting from limitations in our current state of scientific understanding. Therefore, risk-assessment guidelines should be just that—guidelines, not requirements. EPA should give specific long-term attention to ways to improve this process, including changes in guidelines.

Process for Public Review and Comment

EPA does not always provide a method by which industry, environmental groups, or the general public can raise questions regarding the scientific basis of a decision made by EPA during the risk-assessment process.

- EPA should provide a process for public review and comment with a requirement that it respond, so that outside parties can be assured that the methods used in risk assessments are scientifically justifiable.

Petitions for Departure from Default Options

EPA does not have a procedural mechanism that allows those outside EPA to petition for departures from default options.

- EPA should develop a formal process to allow those outside the agency to petition for departures.

Iterative Uncertainty Analysis

Because EPA often fails to characterize fully the uncertainty in risk assessments, inappropriate decisions and insufficiently or excessively conservative analyses can result.

- The committee believes that the uncertainty in a risk estimate can be handled through an iterative process with the following parts: conduct a conservative screening analysis, conduct a default-uncertainty analysis, and conduct testing or analysis to develop site-specific probability distributions for each important input. The key factor in deciding to increase the intensiveness of uncertainty analysis should be the extent to which changes in estimates of costs and risks could affect risk-management decisions.

Risk Assessment vs. Risk Management

The principle of separation of risk assessment from risk management has led to systematic downplaying of the science-policy judgments embedded in risk assessment. Risk assessment accordingly is sometimes mistakenly perceived as a search for "truth" independent of management concerns.

- EPA should increase institutional and intellectual linkages between risk assessment and risk management so as to create better harmony between the science-policy components of risk assessment and the broader policy objectives of risk management. This must be done in a way that fully protects the accuracy, objectivity, and integrity of its risk assessments—but the committee does not see these two aims as incompatible. Interagency and public understanding would

be served by the preparation and release of a report on the science-policy issues and decisions that affect EPA's risk-assessment and risk-management practices.

Comparisons of Risk

EPA often does not elucidate all relevant considerations of technical accuracy when it compares and ranks risks.

- EPA should further develop its methods for risk comparison, taking account of such factors as differing degrees of uncertainty and of conservatism in different categories of risk assessment.

Policy Focus on Stationary Sources

Title III focuses primarily on outdoor stationary sources of hazardous air pollutants and does not consider indoor or mobile sources of those pollutants.

- EPA should clearly communicate to Congress that emissions and exposure, and thus the aggregate risk to the public, related to indoor and mobile sources might well be higher than those related to stationary sources.

Risk Management and Research

EPA does not appear to use risk assessment adequately as a guide to research and might abandon some important risk-assessment and regulatory efforts prematurely because of data inadequacies.

- The conduct of risk assessment reveals major scientific uncertainties in a highly systematic way, so it is an excellent guide to the development of research programs to improve knowledge of risk. EPA should, therefore, not abandon risk assessments when data are inadequate, but should seek to explore the implications for research. Risk-assessment uncertainties can also help to determine the urgency with which such research should be developed. In particular, improved cooperation between EPA's Office of Air Quality Planning and Standards (OAQPS) and its Office of Research and Development (ORD) through such actions as joint publication of a research agenda on hazardous air pollutants would be most helpful.

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Appendixes

NOTE: The following appendixes have been typeset from a variety of original sources. The typographical appearance of the originals, as well as the editorial content and style, has been preserved wherever possible.

Appendix A

Risk Assessment Methodologies: EPA's Responses to Questions from the National Academy of Sciences

Disclaimer

This document was prepared primarily by the staff of the Pollutant Assessment Branch within the Office of Air Quality Planning and Standards. Some of the responses that describe future risk assessment procedures and policies represent the opinions of the authors within the Office of Air Quality Planning and Standards and do not necessarily represent the U.S. Environmental Protection Agency policy.

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Question 1: What Does EPA Consider To Be the Risk Assessment Requirements Needed To Implement the Clean Air Act of 1990?

I.A. Introduction

Implementation of Title III of the Clean Air Act (CAA) requires the development and consideration of risk and hazard assessment in several provisions. The extent of assessment appropriate for each implementation activity is dependent on various factors. These include, but are not limited to, the purpose of the specific provision, the statutory timing and relationship to other provisions, and the availability of data and analytical methods. The next sections describe the regulatory flow and timing of Title III implementation, identify the levels of assessment and review, and describe the provisions with risk-related requirements.

I.B. Regulatory Flow and Chronology of Title III Implementation

Regulation under Title III is comprised of two major steps: the application of technology-based emission standards to categories of major stationary industrial sources, followed by the evaluation of residual risks and the development of further standards, as necessary, to insure that public health is being protected with an ample margin of safety. Affected source categories are identified based on emissions of listed pollutants. The list of source categories and agenda for regulation are required to be published. Extensions from compliance with the technology-based standards are available with demonstration of voluntary emissions reductions, documented problems with the installation of controls, or recently installed controls. Following compliance with the technology-based standards (maximum achievable control technology or MACT), EPA is required to evaluate residual risks and promulgate further standards, if necessary. Compliance and enforcement of the regulations is implemented through an operating permit program at the State level. The flow of the regulatory program under Title III is summarized in Figure 1.

In addition to the regulatory requirements, there are a number of studies in Title III that require reports to Congress on various schedules. The timing of these studies and the principal regulatory milestones are illustrated in Figure 2.

I.C Levels of Risk Assessment

Table 1 presents a brief overview of those Title III provisions which contain elements of risk assessment. Included is a categorization of the level of analysis associated with each activity and the level of review. These are briefly described below. Their use, as exemplified in the past and present or future efforts is presented in the response to Question 2.

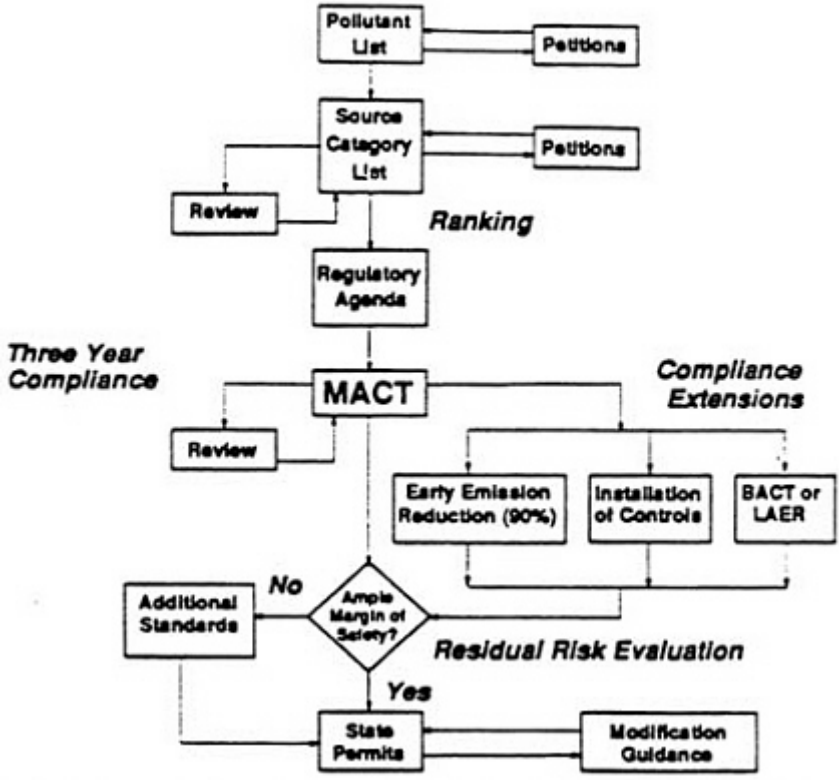

FIGURE 1 Title III Regulatory Flow.

a. Problem Definition: Problem definition activities generally include scoping studies to broadly assess the potential magnitude of the air toxics problem.

b. Hazard Assessment: A hazard assessment is the evaluation of the potential of a substance to cause human health or environmental effects. It would include an assessment of the available effects data and additional information such as environmental fate, potential for bioaccumulation, and identification of sensitive subpopulations.

c. Hazard Ranking: A hazard ranking is the relative comparison of information identified in individual pollutant hazard assessments. The purpose of this type of analysis is to rank or group pollutants that pose similar hazards to public health or the environment.

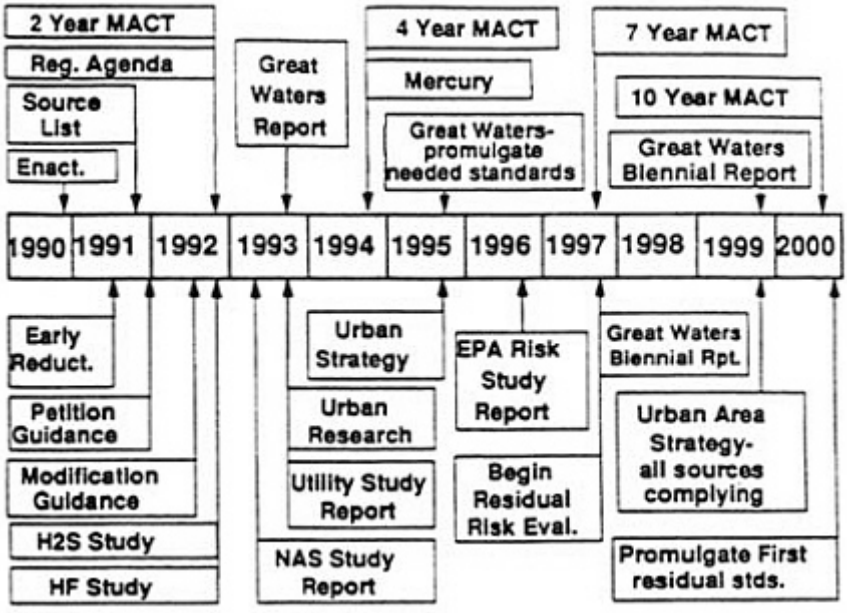

FIGURE 2 Chronology of Title III Risk-Related Activities.

d. Risk Ranking: A risk ranking is the comparative ranking that considers both emissions or exposure information and health effects data. The data may vary in quality depending upon the needs of the specific project.

e. Quantitative Risk Assessment: Quantitative risk assessment is the quantitative characterization of individual and population risk. It is typically conducted for individual sources, but the results may also be aggregated across an industrial source category. This level of analysis requires the most extensive collection of data and analytical resources.

I.D Risk Assessment Review Requirements

The assessments and methods used to implement various aspects of the air toxics program undergo a series of internal and external review procedures. The level of the review varies but will generally fall into one or more of the categories. The levels of review intended for each implementation activity under Title III are indicated in Table 1 and are broadly described below. It should be noted that individual components of a risk assessment may have a formal peer review.

For example, hazard assessment documents always undergo external peer review.

a. Internal Review: This generally consists of review by EPA technical and scientific staff, supervisors, and senior management. It may also include review by Agency-wide committees such as the Risk Assessment Forum (RAF) or the Risk Assessment Council (RAC). Internal review is included in all phases of regulatory and methods development.
b. External Review by Individuals: This review is conducted by individuals outside the Agency who are selected for their expertise in a specific area.
c. External Review by Panels: Such review is the result of a workshop or meeting of experts and representatives of interested groups or affected organizations.
d. Public Review: This consists of review by the public of all supporting documentation as part of the formal rulemaking process, and follows publication of a proposed rule in the Federal Register.
e. Formal External Review: This is review by established advisory committees (e.g., EPA's Science Advisory Board (SAB), National Academy of Sciences (NAS), National Air Pollution Control Techniques Advisory Committee (NAPCTAC)).[1]

I.E Title III Risk-Related Provisions

Several provisions of Title III contain requirements for risk or hazard assessment. Beginning on the following page, Table 1 summarizes these provisions. The levels of analysis and review identified on the Table correspond to the levels discussed above. The codes used in the Table are explained in notes on the last page of the Table.

[1] The NAPCTAC is a committee composed of representatives of industry, environmental groups, and State and local agencies. It was established pursuant to Section 117 of the CAA. The primary focus of NAPCTAC is the review of control technology alternatives considered in the development of emission standards. The role has expanded to include other areas relevant to Title III implementation.

Table 1: Overview of CAA Title III Risk-Related Requirements

Statutory Cite / Project Description	Statutory Deadline	Data Considered for Finding	Level of Analysis[1]	Level of Review[2]
Section 112(a) Lesser Quantity Emission Rates - modification of major source definition based on potency, persistence, bioaccumulation potential, other characteristics of a pollutant, or other relevant factors - EPA currently considering implementation options	- discretionary activity	- sufficient data to identify critical health effect(s) - estimate of risk based on generic exposure modeling - consideration of bioaccumulation	RR	a,c,d
Section 112(b) Pollutant Listing and Delisting - modification of hazardous air pollutant (HAP) list by EPA on own accord or following petition - listing of HAP requires demonstration that emissions, ambient concentrations, bioaccumulation, or deposition of substance is known or reasonably anticipated to cause an adverse human health or environmental effect - delisting of HAP requires opposite demonstration - EPA currently drafting guidance for petitioners	- periodic review of list - response to petition within 18 months of receipt	- identification of known or reasonably anticipated adverse effect(s) Hazard data: sufficient to identify critical effect(s) Exposure data: sufficient to identify potential exposures	RR	a,d,e

Statutory Cite/Project Description	Statutory Deadline	Data Considered for Finding	Level of Analysis[1]	Level of Review[2]
Section 112(c) Source Category List (Delisting) - modification of source category list by EPA on own accord or following petition - max. individual cancer risk from any I source cannot $>10^6$ - noncancer risks: must protect public with "ample margin of safety" - consideration of environmental effects included - EPA currently drafting guidance for petitioners	- development of list within 12 months; list proposed 6/91 - response to petition within 12 months of receipt	- identification of effects and exposure as listed above - potential exposures may be assessed using tiered approach with increasing data requirements	QRA	a,d
Section 112(e) Source Category List (Schedule) - identification of categories to be covered by standards promulgated within 2, 4, 7, or 10 years - priorities to consider known or anticipated health and environmental effects, quantity and location of emissions, and potential for grouping categories	- publish schedule, Nov '92	- screening assessment using available effects and exposure data to assess relative ranking of source categories	RR	a,d

Statutory Cite/Project Description	Statutory Deadline	Data Considered for Finding	Level of Analysis[1]	Level of Review[2]
Section 112(f) Residual Risk - evaluation of risks associated with emissions following implementation of control technology standards promulgated under Section 112(d) - EPA/Surgeon General report to evaluate methods for evaluating health risks, significance of residual risks, additional control options and associated costs, uncertainties associated with analysis, and recommended legislative changes - default, if Congress does not act on recommended legislative changes, is to use previous methods (e.g., benzene decision)	- EPA/Surgeon General report, Nov '96 - promulgation of additional standards within 8 years of Section 112(d) standards	- characterization of effect(s) with quantification of exposure and dose-response - consideration of individual and population risks	QRA	a,d,e
Section 112(g) Modifications - identification of relative ranking of HAPs based upon potential to elicit health effects considering threshold and nonthreshold effects - ranking to be considered in evaluating emission offsets - establishment of de minimis levels	- guidance, May '92	- ranking using available effects data to assess relative toxicity of the HAPs and establish de minimis levels	HR	a,c,d,e

Statutory Cite/Project Description	Statutory Deadline	Data Considered for Finding	Level of Analysis[1]	Level of Review[2]
Section 112(i) Early Reduction Program - extension of compliance with control technology standards allowed - special consideration of "highly toxic" pollutants	- proposed rule, Jun '91 - final rule, Spring '92	- establishment of highly toxic pollutants similar to Lesser Quantity Emission Rates program identified above	HR	a,c,d,e
Section 112(k) Urban Area Source Program - development of research program on the sources of HAPs in urban areas - identification of ≥ 30 HAPs and associated source categories that pose the greatest threat to public health in urban areas - development of national strategy, accounting for ≥ 90% of the identified HAP emissions, resulting in ≥ 75% reduction in cancer incidence	- report to Congress on research activities, Nov '93 - report to Congress on national strategy, Nov '95 - implement strategy such that sources are in compliance, '99	- analysis of urban exposures using ambient monitoring data and modeling of estimated emissions - sufficient data to identify critical effect(s) and dose-response relationships	RR, QRA	a,b,c,c (d, as needed)

Statutory Cite/Project Description	Statutory Deadline	Data Considered for Finding	Level of Analysis[1]	Level of Review[2]
Section 112(m) Great Waters Study - investigation of the contribution of atmospheric deposition of HAPs to the Great Lakes, Chesapeake Bay, Lake Champlain, and coastal waters - development of regulations as necessary to prevent adverse health and environmental effects	- establish Great Lakes monitoring network, Dec '91 - report to Congress, Nov '93 - promulgation of additional regulatory measures, Nov '95	- sufficient data required to identify critical HAPs, potential exposures and critical effects - key parameters to consider include: environmental persistence, bioaccumulation potential, delineation of contribution of air emissions vs. other sources of pollutants	RR, QRA	a,b,c,c (d, as necessary)
Section 112(n) Electric Utility Study - evaluation of public health risks associated with HAPs emitted from electric steam generating units following implementation of Title IV (acid rain) regulations - report on alternative control strategies, if needed	- report to Congress, Nov '93	- sufficient data to identify critical HAPs, their exposures, potential and initial effects - assess individual and population risk	QRA	a,b,c

Statutory Cite/Project Description	Statutory Deadline	Data Considered for Finding	Level of Analysis[1]	Level of Review[2]
Section 112(n) NIEHS Study of Mercury - establishment of threshold concentrations of mercury	- report to Congress, Nov '93	- sufficient hazard and dose-response data relevant to establishing a threshold concentration for mercury	HA	b,c (possible)
Section 112(n) Mercury Study - evaluation of mercury emissions from utilities, municipal waste combustors, and other sources	- report to Congress, Nov '94	- identify health and environmental effects	RR	a,b
Section 112(n) Hydrogen Sulfide Study - assessment of public health and environmental hazards associated with emissions from the extraction of oil and natural gas - development and implementation of control strategy, as needed	- report to Congress, Nov '92	- sufficient evidence on health and environmental effects - adequate emissions data from the oil and natural gas industry	RR	a,b,(d, as needed)

Statutory Cite/Project Description	Statutory Deadline	Data Considered for Finding	Level of Analysis[1]	Level of Review[2]
Section 112(n) Hydrofluoric Acid Study - assessment of the potential health and environmental hazards of HF emission releases including worst case accidental releases - recommendation for reducing hazards, if appropriate	- report to Congress, Nov '92	- sufficient evidence on health and environmental effects - adequate emissions data and probability of accidental release events	RR	a,b,(d, as needed)
Section 112(0) National Academy of Sciences Study - review of EPA risk assessment methods - exploration of opportunities to improve current methods	- report to Congress, May '93	- all data considered relevant by the committee		e

Statutory Cite/Project Description	Statutory Deadline	Data Considered for Finding	Level of Analysis[1]	Level of Review[2]
Section 112(r) Accidental Release Program - identification of principal pollutants (≥ 100) and associated threshold quantities - pollutant petition process included - establishment of Chemical Safety Board - development of regulatory program	- report to Congress on use of hazard assessments, May '92 - promulgation of pollutant list and threshold quantities, Nov '92 - report to Congress on regulatory recommendations, Nov '92	- identification of potential for death, injury, serious adverse effect(s)	QRA	a,d,e

[1] Levels of Anaylsis: HA, Hazard Assessment; HR, Hazard Ranking; RR, Risk Ranking; QRA, Quantitative Risk Assessment, as described in Section I.C.
[2] Levels of Review as described in Section I.D.

II. Question 2: What has EPA done in the past toward those or similar risk assessment requirements, and why did EPA take the specific actions it did?

II.A Introduction

The following sections describe the framework for risk assessment presented by specific activity. The first section describes these activities generically, and subsequent sections provide examples of past and current or planned assessments.

II.B Generic Discussion

The approach EPA follows in conducting risk assessments follows the framework proposed by the National Research Council (NRC) of the National Academy of Sciences in 1983. This process was described in a book entitled "Risk Assessment in the Federal Government: Managing the Process" and identified risk assessments as containing one or more of the following four components: hazard identification, dose-response assessment, exposure assessment, and risk characterization.

In response to the NRC proposal, EPA issued several risk assessment guidelines addressing such areas as carcinogenicity, developmental toxicity, chemical mixture assessment, reproductive toxicity, exposure assessment, and mutagenicity. The EPA is continuing to develop guidelines to address various issues including risk assessment methods for evaluating noncancer effects, e.g, guidelines discussing immunotoxicity and respiratory toxicity.

The sections that follow generally discuss the process of developing risk assessment guidelines and provide examples of the efforts undertaken by the Agency to address the four components of the risk assessment process. For instance, the hazard identification and dose-response assessment steps are incorporated into the development of the hazard assessment documents.

II.B.1 Risk Assessment Guideline Development

The EPA has published guidelines addressing various aspects of risk assessment to direct the Agency in the consistent evaluation of environmental pollutants. The process of developing Agency-wide risk assessment guidelines is a multi-year procedure incorporating the state-of-the science with both internal and external expertise. This process is illustrated in Figure 3. The guidelines serve two purposes: (1) to guide EPA scientists in conducting Agency risk assessments and (2) to inform EPA decision makers and the public about these procedures. The principles set forth in the EPA risk assessment guidelines apply across all risk-based decisions considered by the Agency.

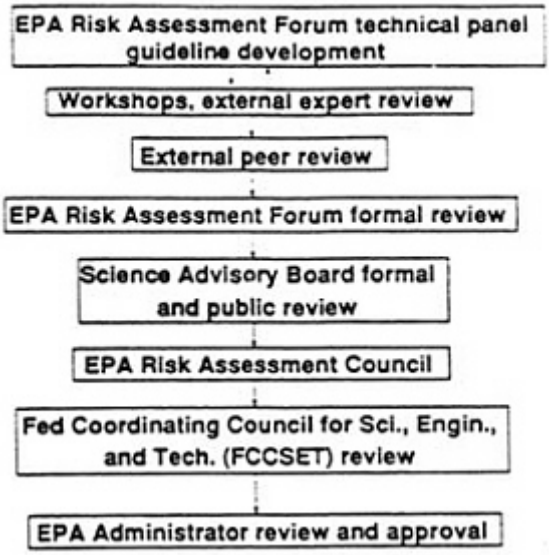

FIGURE 3 Risk Assessment Guidelines Development Process.

The emphasis of these guidelines is that the risk assessments should be conducted on a case-by-case basis considering all relevant information. The information considered includes: the level of analysis required to meet the needs of the risk manager, the availability of data, and the existing methods for appropriately interpreting the scientific data. The guidelines also stress the need to clearly articulate the scientific basis and rationale for each assessment along with its associated strengths and weaknesses. Included must be a description of the uncertainties, assumptions, and limitations of the risk assessment conducted.

II.B.2 Hazard Assessment Document Development

Hazard Assessment Documents (HADs) were commissioned at the request of EPA's Office of Air Quality Planning and Standards (OAQPS) to provide health information on the 30+ substances that were being considered for listing under section 112 of the Clean Air Act in the 1980's. In 1982, an EPA Office of Research and Development (ORD) committee was convened for the purposes of developing a plan for producing hazard assessment documents. They were specifically charged with determining the scope and content of the documents, procedures for production and peer review, and the schedules and resources necessary for production within the anticipated deadlines.

The most immediate purpose of the documents was to meet the needs of OAQPS by providing critical evaluations of all the pertinent health literature and data to determine whether or not significant human health effects were associated with exposure to chemicals at ambient air concentrations. The committee agreed these should focus on air-related health concerns, but attempts would be made to identify other EPA program offices as potential users, requiring the structure of the documents to consider multi-media assessments. The contents of each document would consider:

- physical and chemical characteristics
- man-made and natural sources and emissions
- environmental distribution and measurement, including measurement techniques, transport and fate, environmental concentrations and exposures (multi-media)
- ecological effects
- biological disposition, metabolism, and pharmacokinetics
- toxicological overview of health effects
- specific health effects, i.e., mutagenicity, carcinogenicity, and other noncancer health effects
- synergism and antagonism
- health risk information
-

A multi-tiered assessment approach was employed, with successively more detailed and extensive assessments conducted as warranted by preceding outcomes. The results of each level would be reviewed by the program office (OAQPS) and considered along with exposure assessment information developed by OAQPS in order to determine the necessity for further, more detailed assessment. The process is diagrammed below in Figure 4.

II.B.3 Exposure Methodology

The first systematic exposure assessments of hazardous air pollutants (HAPs) began as a result of provisions in the Clean Air Act of 1970 requiring the identification and listing of HAPs, as well as the promulgation of emissions standards for those listed HAPs. To assist in these assessments, the Human Exposure Model (HEM) was developed by OAQPS for use as a screening model in the identification and national assessment of candidate HAPs. This role expanded in the early 1980's to include more detailed quantitative evaluation of health risks (principally cancer) associated with stationary emission sources of HAPs.

In 1986, EPA published guidelines on conducting exposure assessments. The guidelines were developed to assist future assessment activities and encourage improvement in those EPA programs that require, or could benefit from, the use of exposure assessments. The authors of the guidelines also attempted to

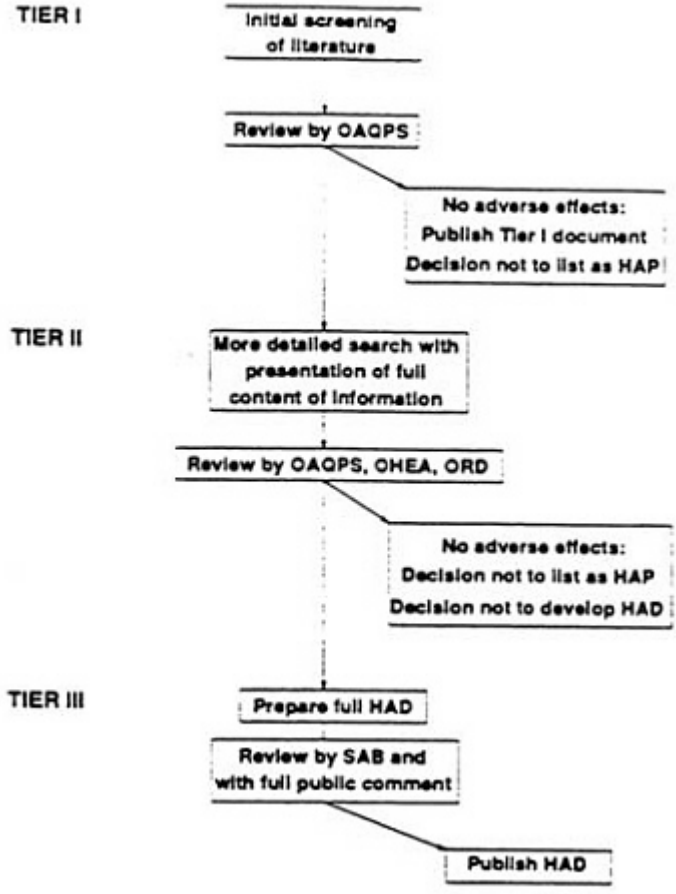

FIGURE 4 Hazard Assessment Document Development.

promote consistency among various exposure assessment activities that are carried out by the Agency. The guidelines recognized that the main objective of an exposure assessment is to provide reliable exposure data or estimates for a risk characterization. Since a risk characterization requires coupling exposure information and toxicity or effects information, the exposure assessment process should be coordinated with the effects assessment. The OAQPS has interpreted this important consideration to mean a balancing of uncertainties in the exposure assessment with the uncertainties in the effects assessment, i.e., quality toxicity assessments are supported with quality exposure assessments. In 1991, EPA revised the exposure assessment guidelines to substantially update the earlier

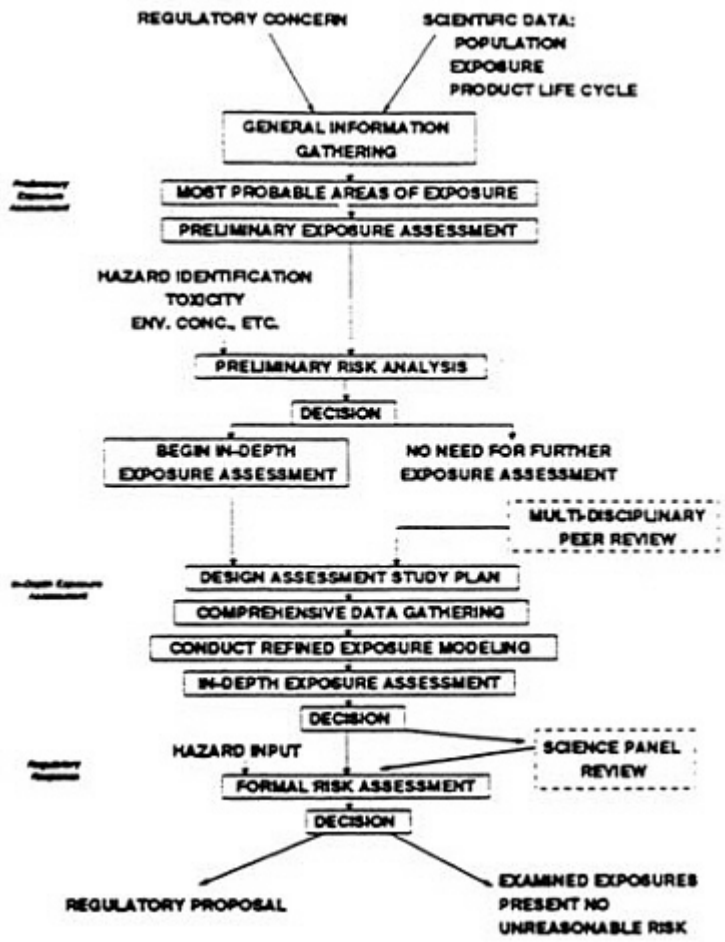

FIGURE 5 Integration of Exposure Assessment into Risk Assessment Process.

guidelines. The new guidelines incorporate developments in the exposure assessment field since 1986, both including the previous work and adding several topics not covered previously. The EPA will be examining the exposure assessment process for HAPs to ensure consistency with the new guidelines. Figure 5 presents a diagram of the process.

II.B.4 Risk Characterization and Treatment of Uncertainty

One of the issues which EPA continues to address has been the characterization and communication of estimated risks and their uncertainties to a variety of

audiences, including Agency risk managers, State and local air pollution control agencies, the public, the affected industries, environmental groups, and other interested parties. The OAQPS traditionally conducted risk characterizations nationally by source category, rather than presenting risks posed by each emission point or facility. In the early 1980's risk estimates were used largely to rank source categories by their estimated potential risks. As experience was gained with risk assessments and the perceived need of risk managers to have more information to make more informed decisions increased, the national source category approach evolved into plant-by-plant and, in some cases, emission point-by-emission point analyses.

The process of risk characterization combines the results of the hazard identification, dose-response assessment, and exposure assessment. In evaluating HAPs, EPA reviews the available information and determines the most appropriate level of risk estimation that may be conducted using these data. The data generally can be categorized into four areas: (1) source and emissions; (2) transport of the pollutant from the source to the target population; (3) exposure of the target population; and (4) adverse effects resulting from the exposure. Depending upon the quantity and quality of the data, the risk assessment may be qualitative and/or quantitative in nature.

Qualitative risk assessments include an analysis of the existing data base and the potential for the pollutant to elicit an effect in a population. This assessment may involve the classification of the data into weight-of-evidence categories and would include a consideration of the severity of the effect anticipated in the exposed population.

Quantitative cancer risk assessments have frequently included the presentation of information in three ways: (1) estimated population risk, expressed as average annual incidence; (2) maximum individual lifetime risk; and (3) distribution of individual risk across the exposed population, i.e., the number of individuals at risk in various risk intervals (e.g., 10^{-4}, 10^{-5}, 10^{-6}).

The evaluation of potential noncancer risks has frequently involved the comparison of estimated ambient levels with a reference level. For example, the risk for developmental toxicity may be inferred by comparing the reference dose for this effect (RfDDT) and the human exposure estimate or by calculating the "margin of exposure" (MOE). The RfDDT, derived by applying uncertainty factors to the no observed adverse effect level (NOAEL) (or the lowest observed adverse effect level, LOAEL), differs from the RfD because the former is based on a short duration of exposure rather than chronic exposure situations. The MOE is the ratio of the NOAEL from the most appropriate or sensitive species to the estimated human exposure level, and is presented along with a discussion of the

weight-of-evidence (WOE) classification. The WOE incorporates information from all relevant studies and represents a judgment based on the collective database as to the likelihood that exposure to a specific substance may pose a risk to humans. Placing an agent in a particular WOE category such as "adequate evidence for human developmental toxicity" does not mean that it will be a developmental toxicant at every dose, since the Agency assumes the existence of a threshold for the effect. Appendix A presents additional information on EPA's risk assessment guidelines for developmental toxicity.

As tools develop in the area of noncancer risk assessment along with expansion of existing data bases, quantitative presentation of risk assessments similar to analyses conducted for potential carcinogenic risks may be possible. It should be noted that the presentation of either a qualitative or quantitative risk assessment must always be accompanied by a description of the limitations associated with the analysis including attendant assumptions and uncertainties.

As risk managers seek to derive the maximum information possible for decision-making, greater emphasis has been placed on the characterization of uncertainty. The key uncertainties associated with the overall risk assessment process can be divided into three areas: uncertainties in the quantification of health effects; uncertainties in modeling the atmospheric dispersion of emitted HAPs; and uncertainties in the assessment of population exposure. Uncertainties associated with health effect quantification arise from use of the linear multistage model for estimating cancer potency, extrapolation from high-dose to low-dose, extrapolation from animal to sensitive human populations and extrapolation across various routes of exposure. A critical need is to expand our understanding about the relevant underlying physical, chemical, and biological mechanisms that affect the validity of extrapolation assumptions. Uncertainties associated with atmospheric dispersion modeling stem from uncertainties in emission rates, meteorological and terrain information, and relation of assumed stack parameters and locations to actual values. Uncertainties in the assessment of population exposure arise from uncertainties in the location and activity patterns of exposed populations, duration of actual exposures in each microenvironment, and extrapolations across exposure conditions. Appendix P includes a chart which illustrates the expected magnitude of uncertainties surrounding several exposure parameters evaluated in the assessment of benzene emissions. Activities within EPA to reduce the uncertainties in each of these areas are described later in the section on evolution of exposure and risk assessment methodologies (II.D.6).

II.B.5 Some Differences Between Past and Present Risk Assessment

The new CAA expands the scope of air toxics regulations. Consequently, expectations at each level of assessment have increased. For example, hazard

assessment and hazard ranking currently place greater focus on the relative hazard and potency of the effects. Exposure information and emission data are also subject to this increased level of need. For example, the Toxic Release Inventory (TRI) data base, established under Section 313 of the Superfund Amendments and Reauthorization Act (SARA), contains emission data on many HAPs, but the data are generally not sufficient to use in quantitative risk assessments. The data base is limited in that it only covers certain industrial types, and is required only for relatively large plants. While this type of information may have been useful for defining a problem or to derive crude estimates of exposure in the past, it is not anticipated to be sufficient for quantitative risk assessments.

The questions and needs to be addressed under the CAA go beyond the data issue. The assessment procedures of the past will have to be reexamined in light of the new legislation. Requirements associated with the residual risk determinations bring about additional concerns for the quantitative risk assessment process. Some of these concerns are:

- assessing residual risk from multiple pollutants rather than individual pollutants within a source category
- determining the approach appropriate to evaluating risk to the most exposed individual
- assessing noncancer health risks
- determining the risks from less than chronic exposure, especially acute exposures
- factoring population mobility and activity patterns into the risk assessment process
- identifying sensitive populations
- assessing ecological risks

While these may not be new concerns, the CAA of 1990 has focused greater attention on these issues.

II.C Examples of Past Assessments

II.C.1 Problem Definition

Exposure to HAP emissions may result in a variety of adverse health effects considering both cancer and noncancer endpoints. In an effort to better understand the "big picture" of hazardous air pollutant exposures, EPA undertook broad, screening studies in the 1980's to evaluate the releases of these pollutants and the relative implication of the resulting exposures to human health.

One study, entitled "Cancer Risks from Outdoor Exposure to Air Toxics"

(Appendix B), assessed the magnitude and nature of potential cancer risks associated with exposure to hazardous air pollutants. Originally conducted in 1985 and updated in 1990, the work broadly assessed long-term exposures to HAPs and estimated potential cancer risks associated with these pollutants. The results of the updated analysis estimated an increase of cancer cases to be between 1700 and 2700 per year as a result of HAP exposure. Approximately 40 percent of these cases were associated with emissions from stationary sources versus mobile sources. In addition, maximum individual cancer risks were estimated to be in excess of 1 in 1,000 at several locations.

II.C.2 Hazard Assessment

A hazard assessment as defined by EPA guidelines is an evaluation of a chemical's toxicity and potential to cause adverse health and environmental effects. At minimum, it entails a search of the scientific literature and an assessment of the amount and quality of the data including the availability of dose-response data.

A qualitative assessment of data includes evaluation of available human, animal, and in vitro evidence in determining how likely a chemical is to elicit an adverse effect in humans or other exposed populations of interest. This type of information is generally examined within the framework of a weight-of-evidence classification scheme.

If sufficient quantitative data are available, a dose-response assessment may be conducted. For carcinogens, the Agency has traditionally developed unit risk estimates (UREs) to express the relationship between dose and carcinogenic response. An URE, under assumption of low-dose linearity, is an estimate of the excess, lifetime risk due to continuous exposure to one unit of concentration (e.g., ug/m^3 for inhalation). For noncarcinogens, limited data and risk assessment methods allowed only the identification of effect levels rather than a quantitative expression of the data.

In addition to toxicity data, other information that is typically included in a hazard assessment include data on a chemical's environmental fate, transport, or persistence in the environment. If the data are sufficient, a hazard assessment presents a profile of a chemical's toxicity, potential health and environmental risk, and related chemical characteristics. In practice, this is best exemplified by HADs (see discussion in Section II.B.2). The HADs incorporate all of the information listed above. These documents also undergo a peer-review by EPA's Science Advisory Board (refer back to Figure 4). This type of assessment formed the principal basis for decisions to list chemicals as HAPs under the previous Section 112.

II.C.3 Hazard Ranking

There are no past examples of hazard ranking. Rankings that were done used emission data to rank rather than toxicity data which, for the most part, lacked sufficient potency data to do adequate ranking.

II.C.4 Risk Ranking

Figure 6 illustrates the process used to identify HAPs prior to passage of the Clean Air Act Amendments of 1990. During the mid-1980's, the Agency modified this process to add in the "Intent-to-List" procedure prior to actually listing a chemical under Section 112 of the CAA. Table 2 identifies the pollutants that EPA formally evaluated during this time frame and the resulting decision to continue analysis (intent-to-list) or discontinue analysis (not-to-regulate). Examples of the notices published in the *Federal Register* are included in Appendix C.

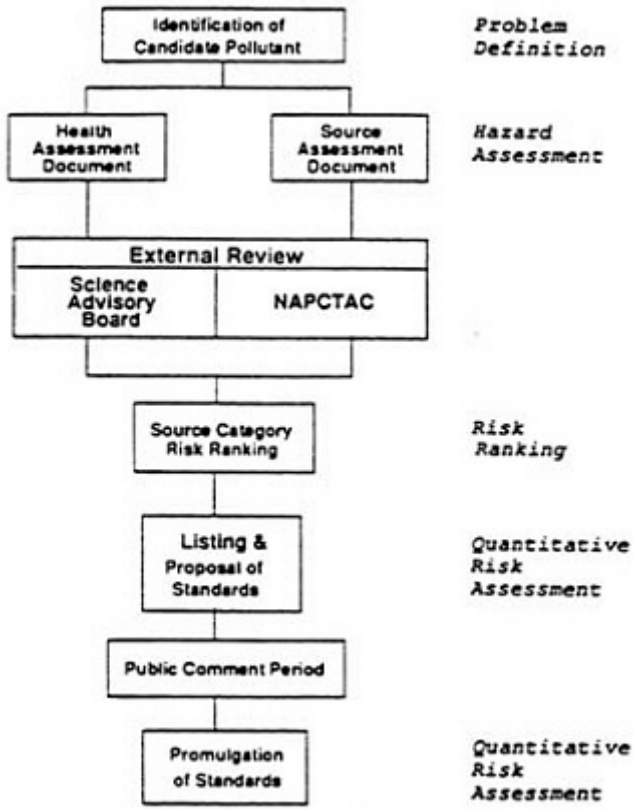

FIGURE 6 Identification, Assessment, and Regulation of HAPs.

TABLE 2 1984-1987 Hazardous Air Pollutant Decisions

POLLUTANT	ACTION	CITATION
Acrylonitrile	State Referral	50FR24319; June 10, 1985
1,3-Butadiene	Intent-to-List	50FR41466; October 10, 1985
Cadmium	Intent-to-List	50FR42000; October 16, 1985
Carbon Tetrachloride	Intent-to-List	50FR32621; August 13, 1985
Chlorofluorocarbon 113	Not-to-Regulate	50FR24313; June 10, 1985
Chlorinated Benzenes	Not-to-Regulate	50FR32628; August 13, 1985
Chloroform	Intent-to-List	50FR39626; September 27, 1985
Chloroprene	Not-to-Regulate	50FR39632; September 27, 1985
Chromium	Intent-to-List	50FR24317; June 10, 1985
Coke Oven Emissions	Listing Notice	49FR36560; September 18, 1984
Copper	Not-to-Regulate	52FR5496; February 23, 1987
Epichlorohydrin	Not-to-Regulate	50FR24575; June 11, 1985
Ethylene Dichloride	Intent-to-List	50FR41994; October 16, 1985
Ethylene Oxide	Intent-to-List	50FR40286; October 2, 1985
Hexachlorocyclopentadiene	Not-to-Regulate	50FR40154; October 1, 1985
Manganese	Not-to-Regulate	50FR32627; August 13, 1985
Methyl Chloroform	Not-to-Regulate	50FR24314; June 10, 1985
Methylene Chloride	Intent-to-List	50FR42037; October 17, 1985
Municipal Waste Combustion Emissions	Advance Notice of Proposed Rule-making	52FR25399; July 7, 1987
Naphthalene	Not-to-Regulate	53FR9138; March 1, 1988
Nickel	Not-to-Regulate	51FR34135; September 25, 1986
Perchloroethylene	Intent-to-List	50FR52880; December 26, 1985 *51FR7719; March 5, 1986
Phenol	Not-to-Regulate	51FR22854; June 23, 1986
Polycyclic Organic Matter	Not-to-Regulate	49FR31680; August 8, 1984
Toluene	Not-to-Regulate	49FR22195; May 25, 1984
Trichloroethylene	Intent-to-List	50FR52422; December 23, 1985 *51FR7714; March 5, 1986
Vinylidene Chloride	Not-to-Regulate	50FR32632; August 13, 1985
Zinc/Zinc Oxide	Not-to-Regulate	52FR32597; August 28, 1987

*Clarification Notice

II.C.5 Quantitative Risk Assessment: The Regulation of Benzene: 1977-1989

Note: The following sections present an overview of the evolution of risk-based decision-making under the old Section 112, using the regulation of benzene as the principal example. The text is supplemented by several appendices that provide examples of decision documentation and briefing materials from these periods.

Introduction

In June of 1977, EPA added benzene to the list of HAPs under Section 112. For the next twelve years, under a succession of 6 Administrators, the air program wrestled with the regulation of a known human carcinogen for which a health effect threshold could not be established, under an authority requiring the protection of public health with an ample margin of safety. During this period, benzene became the test case for a series of procedural interpretations and reinterpretations of the statutory language, culminating in the 1987 vinyl chloride opinion by the D.C. Court of Appeals (NRDC v. U.S. EPA, July 28, 1987) and the revision of the statute in the 1990 amendments to the Clean Air Act.

The regulation of benzene also spans a period during which the methods for quantitatively estimating risks from exposure to airborne carcinogens evolved, and the appropriate role of such estimates in the decision process was hotly debated within, as well as outside, the EPA. For these reasons, benzene represents an interesting and illuminating case study of quantitative risk assessment and its use in determining the appropriate level of control under Section 112. A chronology of EPA's regulatory policy under Section 112 is summarized in Figure 7.

Benzene and the Airborne Carcinogen Policy (1977-1983)

The EPA listed benzene as a HAP in 1977 based on growing evidence of a link between occupational exposure and an increase in the incidence of acute myelogenous leukemia (Appendix D - Benzene Listing). Prior to the listing of benzene, EPA had regulated four pollutants under Section 112: asbestos, beryllium, and mercury in 1971; and vinyl chloride in 1974-75. In the absence of procedures for estimating cancer risk, the original asbestos standard was based on "no visible emissions". Beryllium had not been identified as a carcinogen (berylliosis was the effect of concern) and the toxic effects of mercury were addressed with an ambient air guideline, taking into consideration exposure by other routes (e.g., ingestion).

Era		*Approach*
1971	**Asbestos** **Beryllium** **Mercury**	**"No Visible Emissions"** **Best Technology** **Ambient Guideline**
1974-75	**Virryl Chloride**	**Best Available Technology (BAT)**
1977-81	**Benzene/Carcinogen Policy**	**BAT/Beyond BAT**
1983-84	**Risk Management**	**Weigh All Factors**
1987	**Virryl Chloride Opinion**	**"Safe"/Ample Margin Of Safety**
1988	**Benzene Proposal**	**"Framing the Debate"**
1989	**Benzene Promulgation**	**"Fuzzy Bright Line"**
1990	**CAA Amendments**	**MACT Now/Residual Risk Later**

FIGURE 7
Chronology of Section 112 Regulatory Policy Development.

By the listing of vinyl chloride in 1974, quantitative techniques were under development within the EPA. In conjunction with the promulgation of the vinyl chloride emission standards, rough estimates of projected incidence of angiosarcoma were made, but were considered too uncertain to be used in the determination. The vinyl chloride standards were principally based on the application of the best available control technology (BAT).

In May of 1976, EPA issued the first carcinogenicity guidelines (Appendix E - "Health Risk and Economic Impact Assessments of Suspected Carcinogens"). In the benzene listing notice the following year, EPA announced the conduct of a benzene health risk assessment and indicated that the "relative risk to the public" would be considered in judging "the degree of control which can and should be required". The risk assessment, containing the original unit risk estimate for benzene, was subsequently published in January 1979 (Appendix F - Benzene Population Risk).

The advent of a quantitative methodology and external pressure for a more aggressive program under Section 112 led to the development of EPA's airborne carcinogen policy. The policy was published in October 1979, as a proposed interpretive rule outlining procedures for the identification, assessment, and regulation

of airborne carcinogens emitted from stationary sources (Appendix G - Airborne Carcinogen Policy). The policy reflected a technology-based approach to emission standard development with a limited role for quantitative risk assessment in establishing priorities and ensuring that the residual risks following the application of BAT were not unreasonable. The first round of benzene standards, beginning with the regulation of maleic anhydride plants in 1980, followed the proposed procedures, the shorthand for which became "BAT/ Beyond BAT". Although a final version of the proposed policy was prepared in 1981, incorporating public comments, the policy was never promulgated. The procedures were informally followed, however, up to the introduction of the "risk management" approach in 1983.

Also in 1979, the development of the Human Exposure Model (HEM) (Appendix H - HEM Description) provided a means of estimating and summing ambient exposures across the populations living in the vicinity of emitting sources. These estimates were then combined with the unit risk estimate to yield cancer risk estimates. In the first benzene standards, estimates of maximum individual lifetime risk and annual incidence were calculated. The risk estimates were sometimes displayed as small ranges, incorporating some of the quantifiable sources of uncertainty. Other uncertainties were usually presented as tabular footnotes (Appendix I - Proposed Maleic Anhydride Standards).

The Risk Management Era (1983-1985)

The change of Administration in 1981 brought an increasing emphasis on the cost-effectiveness of regulation and regulatory reform. In this light, the presumption expressed in the proposed carcinogen policy - that, given the uncertainty in risk estimation, significant source categories of airborne carcinogens should be regulated, at a minimum, to a level of control constituting BAT - was called into question. The re-examination of this presumption resulted in a revised policy which held that risk information, as well as other relevant factors, should be considered in determining the appropriate level of control, including finding that control was unwarranted. One result of this change was to place greater weight on the risk assessment in the decision process.

In 1984, after "weighing all factors", EPA made several changes to the proposed benzene rules, including withdrawal of the maleic anhydride proposal, arguing that the risks were "too small to warrant Federal regulatory action" (Appendix J - Withdrawal of Proposed Standards). These decisions were promptly challenged by the NRDC, arguing the uncertainties in the risk estimates and the inappropriate consideration of cost in regulatory decisions made under Section 112. The issues raised were similar to litigation already pending on amendments to the original vinyl chloride standards.

Also during 1984, work was begun to revise the benzene unit risk estimate, based on new human and animal data and an improved methodology. A revised estimate was transmitted to the air program by the Office of Research and Development in early 1985 (Appendix K - "Interim Quantitative Unit Risk Estimates").

The Vinyl Chloride Opinion (1987)

On July 28, 1987, Judge Robert Bork, writing for the D.C. Circuit Court of Appeals, remanded the vinyl chloride amendments to EPA, finding that the Agency had placed too great an emphasis on technical feasibility and cost rather than the provision of an "ample margin of safety" as required by the statute (Appendix L - Vinyl Chloride Opinion). The opinion also laid out a process for making decisions, consistent with the requirements of the law.

The Bork opinion held that, in setting standards under Section 112, EPA must first determine a "safe" or "acceptable" level, and that this level must be established considering only the potential health impacts of the pollutant. Once an acceptable level was identified, the level could be reduced further, as appropriate and in consideration of other factors, including cost, technical feasibility, affordability, etc., to provide the required ample margin of safety. The Court also held, however, that "safe" did not require a finding of "risk-free" and that EPA should recognize that activities such as "driving a car or breathing city air" may not be considered "unsafe".

Benzene Proposal (1988)

The EPA accepted voluntary remand of the 1984-85 standards and issued a new proposal in July 1988, consistent with the vinyl chloride opinion. Given the requirement for a determination of "safe", the importance of the quantitative risk assessment took on even greater emphasis. This is evident in the senior management briefings on the proposal (Appendix M - Briefing for the Administrator). The determination of a "safe" or "acceptable risk" level continued to be problematic, however, in part due to the diversity of opinion within, and external to, the Agency on what constituted an "acceptable risk" but, also to the dicta of the legal opinion itself. The decision appeared to accept "driving a car or breathing city air" as examples of activities judged to be safe by society. This raises the issue of whether society's judgment to drive or live in cities is founded solely on the possible health impacts of these activities, rather than a consideration of all factors, which would be prohibited in the EPA framework.

Several options for the determination of "acceptable" risk were considered in the months preceding proposal. The preferred option, a case-by-case consideration of all of the relevant health information was described in a memorandum by the Administrator (Appendix N - "Proposed Benzene NESHAP Decisions").

Ultimately, however, EPA proposed four options for the determination of "safe", "framing the debate" for public comment (Appendix O Proposed Benzene NESHAP). With the exception of the case-by-case alternative, the options represented "bright line" risk targets, either individual or population risk. All factors were to be considered in the determination of the ample margin of safety.

Benzene Promulgation (1989)

The EPA received a large volume of comments on the proposed rules. Again, the risk methodology and estimates, and the proposed acceptability criteria were extensively discussed. The appended briefing for the Assistant Administrator (Appendix P - "Consideration of Comments") illustrates the emphasis on the risk methods and underlying uncertainties. During this time, there was also increased interest in not only the estimates of maximum individual and population risk, but also the distribution of individual risk across the exposed population.

In September of 1989, EPA promulgated emission standards for several categories of benzene sources (Appendix Q - Final Benzene Rules). The decision criteria adopted represented a blend of several of the proposed options. The EPA argued for the consideration of all relevant health information and established "presumptive benchmarks" for risks that would be deemed "acceptable". The goal, which came to be known as the "fuzzy bright line", held that risks would be deemed acceptable if few, if any, individuals were exposed above a 1 in 10,000 lifetime cancer risk, and, as much of the exposed population as possible was below a lifetime risk of 1 in 1,000,000.

The selection of even "fuzzy" risk targets placed greater emphasis on the development and communication of risk characterization results. For the final benzene rules, this was evident in the decision briefings as well as the development of question and answer materials (Appendix R - Benzene Questions and Answers) and the decision to provide advance briefings for the news media (Appendix S - Background Information for the Media).

The Clean Air Act Amendments (1990)

The amendments to Section 112 require the application of technology-based standards to major and designated area source categories as a first step. Following compliance with the maximum achievable control technology (MACT) standards, EPA is required to evaluate residual risks, applying the decision criteria used in the final benzene rules, to determine whether the technology-based rules provide an ample margin of safety to protect public health. Risk assessment will continue to play an important role in the implementation of this and other provisions of Section 112 and the importance of appropriate methodologies and characterization of uncertainties cannot be understated.

II.D Examples of Present Assessments

II.D.1 Problem Definition

Sections 112(c) and (k) of Title III prescribe an *Urban Area Source* program that includes the development of a national strategy requiring 75% or more reduction in cancer incidence associated with emissions of 30 or more HAPs that "present the greatest threat to public health in the largest number of urban areas". For this national strategy to be implemented, many issues need to be defined and addressed including:

- types of sources covered
- selection of the urban areas covered
- selection of the 30 or more HAPs to be regulated on a variety of endpoints and characterization of their ambient levels
- characterization of the emission release parameters
- establishment of an emissions inventory system to help demonstrate that the goals of the strategy are being met
- role of atmospheric transformation

This program requires policy decisions as well as research decisions to be made so that the goal of listing the sources in 1995 and promulgating the subsequent standards for affected sources can be met.

The *Great Waters Study* (Section 112[m]), requires that EPA, in cooperation with the National Oceanic and Atmospheric Administration, identify and assess the extent of atmospheric deposition of HAPs to the Great Lakes, Chesapeake Bay, Lake Champlain, and coastal waters. A report to Congress is due within 3 years of enactment and biennially thereafter. A plan is being developed to evaluate the information available, the information needed, and how to acquire that additional information. The Report to Congress requires the following information:

- contribution of atmospheric deposition to total pollution loading
- environmental and public health effects
- sources of the pollutants
- contribution of HAPs to water quality violations

To accomplish this, it will be necessary to:

- conduct atmospheric deposition monitoring for source identification and model validation
- conduct atmospheric transport and deposition modeling to include direct and indirect pathways
- develop emission inventories as input to models
- evaluate adverse effects of air toxics on public health and the environment

The Great Waters work shall also support data sharing and the development of remedial action plans (RAPs) and lakewide management plans (LaMPs). The final results of this study may be the promulgation of further emission standards or control measures as may be necessary and appropriate to prevent the adverse effects from occurring.

II.D.2 Hazard Assessment

With passage of the new CAA, the emphasis on hazard assessment changed from the generation of HADs to the generation of dose-response or potency based estimates where the data supported such an analysis. In selecting appropriated toxicity information, the data required for the statutory findings and mandated deadlines were considered including information on cancer and noncancer effects. For carcinogenic risks, emphasis to date has focused on existing quantitative assessments including unit risk estimates (UREs) (see discussion in Section II.C.2) and ED_{10}s.

The assessment of ambient concentrations of HAPs in relation to their potential to elicit adverse noncancer effects presents several challenges. Considerations must include: evaluation of short-term as well as long-term exposures, incorporation of severity-of-effect data, and consideration of reversible versus irreversible effects. The endpoints that may be of most concern could include respiratory effects, developmental/reproductive toxicity, and neurotoxicity.

The quantification of noncancer risks from exposure to inhaled hazardous air pollutants currently focuses on the derivation of inhalation reference concentrations (RfCs). The RfC is defined as an estimate (with uncertainty) of the concentration that is likely to be without appreciable risk of deleterious effects to the exposed population after continuous, lifetime exposure. The RfC focus is on the most sensitive members of the population who may be exposed and the respiratory system as the portal of entry. An experimental exposure level representing the highest level tested at which no adverse effect was observed (NOAEL) is selected from a given study and converted to a human equivalent concentration ($NOAEL_{HEC}$). The critical toxic effect used is the one generally characterized by the lowest NOAEL. This approach is based on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented. The RfC is derived from the ($NOAEL_{HEC}$) by the application of uncertainty factors to account for extrapolations that may be made. These estimates along with UREs are reviewed within the Agency before incorporation onto EPA's Integrated Risk Information System (IRIS).

Under Title IX of the CAA, EPA is required to develop environmental health assessments for the HAPs. In addition to hazard assessment information, these

profiles are to identify data gaps and, where appropriate, identify the additional activities needed to better characterize the "types or levels of exposure which may present significant risk of adverse effects in humans."

Note: Information concerning revisions to the current EPA's cancer risk assessment guidelines will be provided under separate cover.

II.D.3 Hazard Ranking

A further step in the assessment process is the ranking of HAPs based on their relative hazard to human health. The data needs to be collected in a form which allows the comparison of chemical hazards, e.g. comparing similar endpoints of concern. Ideally, the ranking would rely on Agency-reviewed, benchmark risk values such as UREs or RfCs. In reality, due to the lack of health data, the ranking of chemicals may have to rely on less rigorously reviewed values and many assumptions or defaults. The ranking of HAPs for the purpose of offsets under the modifications section of the CAA (Section 112(g)) provides an example of one approach EPA has taken. This section of the CAA requires that EPA issue guidance which includes the ranking of threshold and non-threshold pollutants. Without sufficient data to the contrary, the EPA currently considers all noncarcinogens as threshold pollutants and carcinogens as non-threshold pollutants. As data become available, this general categorization may change for specific pollutants.

The ranking methodology currently being considered under Section 112(g) uses methods already in place, i.e. for establishing Reportable Quantities under the Comprehensive Emergency Response and Compensation Liability Act (CER-CLA). Non-threshold pollutants (carcinogens) are ranked by comparing potency estimates ($1/ED_{10}$) and weight of evidence classification. The ED_{10}s are defined as the estimated dose associated with a lifetime increased cancer risk of 10%. Threshold pollutants are ranked by either their composite scores (CS) which reflect chronic toxicity, or their level of concern which reflects acute toxicity. Composite scores consider dose-response and severity of effect. The magnitude of the CS determines the ranking position of the chemical (pollutants with large composite scores elicit severe effects at low doses). Under section 112(g), increases in emissions of non-threshold pollutants cannot be offset by decreases in emissions of threshold pollutants, but the reverse is true. The ranking must provide a comparison of the relative hazard within categories of non-threshold and threshold compounds. It is also known that certain pollutants may cause severe effects resulting from acute exposures, therefore the guidance also provides a category for "high concern" threshold pollutants. These pollutants are considered (for the purposes of this section) more hazardous than threshold pollutants but no comparison can be made between these and non-threshold pollutants.

If pollutants do not have adequate data to be ranked as a threshold, non-threshold, or "high concern" pollutant, then that pollutant is considered not tradeable under this section. The general methodology that has been developed to date was reviewed by the Science Advisory Board and National Air Pollution Control Techniques Advisory Committee (NAPCTAC) while the application underwent rounds of internal review and public comment.

II.D.4 Risk Ranking

A number of ongoing activities in Title III are associated with risk ranking, or have risk ranking as one of their components. Under the *Source Category Schedule* development program, the schedule for regulation of the listed source categories due to be published for comment this year, has been primarily based on a risk ranking of the various source categories included on the Section 112(c) list. This ranking process uses the Source Category Ranking System (SCRS), a methodology developed within OAQPS. The SCRS process uses health information, available or estimated emissions data, and population data to develop a numerical score for each category on the list. The scores are then ranked to develop a prioritized list. In general, the SCRS first develops a health score for each pollutant emitted by a source category. The health score for each pollutant is based on available data regarding carcinogenicity, reproductive toxicity, acute lethality, and other toxicity. The SCRS then develops an exposure score for each pollutant emitted by that source category. The exposure score is based on concentration approximations for each pollutant from each facility in the category combined with estimates of the numbers of people exposed to these concentration estimates. General assumptions concerning plant stack parameters, plant boundaries, population densities, and meteorological conditions are made on a category-wide basis to simplify the ranking process. Default assumptions and mass balance emission estimates are used where data are unavailable.

The end result of the SCRS process is not an estimate of risk, but rather a score which indicates the relative magnitude of risks between source categories. This score, along with other factors such as efficiency of grouping like sources for a particular regulation, availability of control technology information, and the specific nature of adverse health effects associated with a source category, is then used to assist in the scheduling of regulations.

The *Lesser Quantity Emission Rate* project is an example of a risk ranking assessment because of the use of exposure assessment and data on health effects. Title III (Section 112(a)) allows the Administrator to establish emission rates for less than 10 and 25 tons/year for HAPs based on their potency, persistence, potential for bioaccumulation, or other relevant factors. The HAPs with UREs and classified as a known, probable, or possible human carcinogen were initially

selected. Added to these were chemicals of high concern under CERCLA. Noncarcinogens were selected on the basis of their inhalation RfC, RfD, LC50, or LOEL. Using standard parameters, a generic exposure modeling was done, including consideration of likely exposure duration. This modeling analysis yielded an estimated ambient concentration at a distance selected to represent the nearest residence. This ambient concentration was compared to cancer UREs or noncancer benchmarks, and HAPs of concern were identified. Lesser quantity emission rates (LQER) were assigned to selected carcinogens based upon order-of-magnitude changes in their potencies. The range of LQERs that resulted was .0001 to 1 ton/year. Selected noncarcinogens were assigned LQERs based on a comparison of the benchmark concentrations with the estimated ambient concentration. The major consequence of this analysis would be a redefinition of some sources as major sources if their emission rates of HAPs exceed the assigned LQER.

II.D.5 Quantitative Risk Assessment

With regard to quantitative risk assessment activities, two current CAA-related activities address the use of refined modeling techniques with site-specific data to quantify risks associated with both longand short-term exposure to hazardous air pollutants from stationary sources.

Source Category Deletion Petition Process

Under Section 112(c), a source category may be deleted from the list of source categories subject to regulation via a petition process if a petition demonstrates, for the case of carcinogenic pollutants, that "no source in the category … emits (carcinogenic) air pollutants in quantities which may cause a lifetime risk of cancer greater than one in one million to the individual in the population who is most exposed to emissions of such pollutants from the source," and, for the case of noncarcinogenic yet toxic polluants, that "emissions from no source in the category … exceed a level which is adequate to protect public health with an ample margin of safety and no adverse environmental effect will result from emissions from any source."

In support of the petition process, EPA is developing guidance for petitioners which suggests acceptable methodologies for assessing cancer and noncancer risk associated with sources of HAPs. This guidance references a document describing a tiered modeling approach for the estimation of maximum risks (see Appendix T - Tiered Modeling Approach). The tiered approach begins with a screening methodology which is used to identify facilities within a source category that do not present risks significant enough to warrant more refined analysis. The screening methodology uses minimal site-specific data (pollutant emission

rates, stack heights, and minimum fenceline distances) in this assessment, and, as such, the results are very conservative. Facilities not screened out in this first tier are subjected to a more refined "Tier 2" assessment requiring additional site-specific information (stack diameters, exit velocities, exist temperatures, rural/urban classification, nearest building dimensions) concerning each modeled facility. The third modeling tier requires the most site-specific data (release point and fenceline locations, local meteorological data, release durations and annual frequencies) to provide the most refined estimate of risks due to each modeled source.

The analyses described above focus on the maximum risks presented by a facility outside its plant boundary, regardless of how many people are subjected to those risk levels. To the extent that population location and distribution data are available, they may be incorporated in the analysis on a case-by-case basis, to provide a more accurate estimate of the risk to the maximum exposed individual.

Residual Risk Evaluation

Under Section 112(f) of the CAA, EPA is required to assess the risks associated with a regulated source category within 8 years of the MACT standard promulgated for that category. The Agency is currently evaluating options for implementing this provision. In investigating various alternatives, many questions have been raised. The EPA is currently exploring many technical and policy issues. These issues must be addressed prior to establishing an implementation strategy for evaluating residual risks.

In fully characterizing the potential risks associated with emissions of HAPs following compliance with the MACT standards, EPA is evaluating the capabilities of current risk assessment methods. Presently, due to limited availability of data and methods, it is difficult to quantitatively characterize specific risks (e.g., noncancr risks). The EPA is evaluating various methods to collect additional effects data (see response to Question 4) as well as exploring the development of new methods and the modification of existing methods to improve the ability to quantify risks. Specific areas that are being explored include: evaluation of less-than-lifetime exposures, incorporation of severity-of-effect data, incorporation of data on reversibility (or irreversibility) of effects, and development of physiologically based pharmacokinetic and biologically based dose-response models.

Currently, it is envisioned that a tiered modeling approach (such as described above in the discussion of the source category deletion process) may be the basis for dispersion modeling associated with residual risk analyses of source categories. The EPA envisions that site-specific emission estimates may "drive"

TABLE 3 Data Sources for Exposure Assessment

DATA TYPES	SCREENING ANALYSES	SITE-SPECIFIC ASSESSMENTS
EMISSIONS AND RELEASE PARAMETERS (STACK HEIGHT, STACK GAS EXIT VELOCITIES)	Engineering estimates. Assume all emissions are emitted from plant center. Use of model plants (e.g., stack heights that typify the emission source). Use of emission factors (AP-42).	Data from industry via Section 114 CAA. Data from source testing, trade associations. Use site plans to place emission where they occur on plant property. Data from permits and plant site visits.
PLANT LOCATIONS (LATITUDE, LONGITUDE)	Some info from EPA data bases (AIRS/NEDS), other sources. Some plants sited by land use or at random.	From industry, topographic maps, site visits.
METEOROLOGY	National Climatic Center data from nearest airport (multiple years averaged to yield annual data sets).	Data collected on site. National Climatic Center data from nearest airport if similar to site.
POPULATION	Latest U.S. Census data. Block Group/ Enumeration Districts, 300,000 data values.	Same. 1990 data will have 6,000,000 data values.
WHERE AMBIENT AIR BEGINS	At 200 meters from assumed plant center (approximately 30 acres).	Use actual plant size or some approximation.
EXPOSURE DURATION	Equal to that of the health information. If effects occur at one hour exposure, predict one hour concentrations/ exposures. For cancer, estimate annual average values that are assumed to persist 70 years (the averaging time of unit risk factor).	Same.
EXPOSURE	Assume indoor concentrations same as outdoor.	Same.

the risk assessment process. Thus, EPA is planning its efforts to expand the available emission measurement methods and validation procedures (validated measurement methods currently exist for only about 15-20% of the listed HAPs). In addition, EPA believes that efforts should be extended to continue to improve available emission calculation methods (emission factors, surface impoundment emission estimation methods, etc.). To assist the process of obtaining sufficient site-specific data for quantitative risk analyses, EPA is investigating options for developing a user-access data entry system. Such a system would necessarily be designed to ease the burden of providing up-to-date data to EPA and to protect against the unauthorized access of proprietary information. Logistics, reporting requirements, and quality assurance associated with such a system are problems with no adequate answers at this point.

The EPA is also looking into improving risk assessments by factoring in more realistic approaches to exposure assessments including consideration of population mobility, population sensitivity, activity patterns, and indoor/outdoor exposures. Because of the intensive data requirements for addressing these factors adequately, sensitivity studies are being considered to assess the ranges of uncertainty induced by each of these factors on the predicted exposures and risks. The results from such studies would hopefully allow a more representative characterization of the distribution of risks among the exposed population in the future.

II.D.6 Evolution of Exposure and Risk Assessment

As previously mentioned, the role and scope of exposure assessments in the air toxics program is changing. Exposure estimates were conducted for two main purposes: 1) to estimate high end and population exposure to a candidate hazardous air pollutant, and 2) to evaluate the effectiveness of various air pollution control alternatives for reducing potential exposure and risk. Table 3 presents data sources and assumptions that were generally used in previous exposure assessments. The source category deletion and residual risk evaluation provisions in Title III place a much greater focus on source and individual exposures associated with an often complex mixture of source types and pollutants.

Procedures that the Agency develops for addressing residual risk will be designed to meet several criteria. State and local air pollution control agencies, affected industries, and private individuals may require access to and familiarity with available models. In addition, the procedure should be able to evaluate present and future control options as interested parties may wish to evaluate residual risk before air pollution control equipment are ordered.

As noted above, OAQPS is currently examining and developing improved techniques for conducting exposure assessments. Although these improvements

will continue to chiefly rely on predictive methods (modeling), measured data, available from monitored levels or reconstructed from measurement of biological fluids and tissues, will remain an important source of information for validation and characterization purposes. The Agency will focus the improvements in three main areas:

1) Developing user-friendly models to enable diverse, interested parties to understand and operate the models if they choose. Data input and selection of specific models will be accomplished by menu screens that contain data checks.
2) Addition of Monte Carlo techniques to permit the representation of those parameters that greatly affect the exposure/risk estimates by distributions rather than point estimates (see Appendix U, Monte Carlo Approach).
3) A geographical information system (GIS) will be integrated with the models to improve the predicted ambient concentrations by incorporation of topography and land use information to aid in selection of appropriate meteorological data and the location of area source categories. In addition, GIS will allow OAQPS to more accurately locate areas where people may reside than is currently possible using U.S. Bureau of Census data alone (See Appendix V, GIS - Application to Exposure Assessment).

The HEM input parameters that can presently be described by distributions include:

- emission rates
- microenvironment concentrations
- time spent in each microenvironment
- information on the length of time people are expected to reside in their primary residences
- the ability to vary the location of the predicted ambient concentrations.

The EPA/OAQPS is also developing a separate model (the Hazardous Air Pollutant Exposure Model [HAPEM]) that examines the impact on exposure of population mobility (e.g., commuting) (see Appendix W, HAPEM - Mobility Considerations).

Since the process of conducting residual risk analyses for all regulated sources of HAPs is anticipated to be a resource-intensive process, the analytical methodology has evolved into a tiered approach, as mentioned above. This differs from most risk assessments performed in the past in that it allows for the incorporation of site-specific data where possible to refine the estimates of population

exposure and risk. Since it will likely be difficult for EPA to require all regulated facilities to provide all of the necessary data for such site-specific analyses, EPA has plans to develop a voluntary data storage and retrieval system, whereby such facilities may provide site-specific data to EPA to facilitate the more rigorous risk assessment process. This will not only help EPA to perform residual risk analyses in a more efficient manner, but it will reduce the level of "unnecessary" conservatism associated with the risk assessment process. In situations where EPA does not have site-specific modeling parameters, the risk assessments will be performed at the Tier 1 level, consistent with risk assessments of the past. In situations where additional data have been provided by the facilities being analyzed, risk assessments will be more realistic, and risk estimates will generally be lower (sometimes by orders of magnitude).

Table 4 below summarizes the major differences between the 3 modeling tiers discussed above by briefly listing the input requirements, the major output parameters, and the assumptions associated with each tier. This table may be used to quickly determine whether a given scenario may be modeled at any particular tier based on available site-specific data. Within each tier, cancer unit risk estimates, chronic noncancer concentration thresholds, and acute concentration thresholds are required to convert concentration predictions into cancer risks, chronic noncancer risks, and acute noncancer risks, respectively.

In general, to perform a site-specific exposure assessment, Tiers 1 and 2 could be used to screen facilities with low risk estimates from further analysis at a higher Tier. In cases where facility-specific data are lacking, emissions estimates could be made using a model plant approach with emission factors or process engineering estimates of emissions. In such cases, all known or estimated emissions could be assumed to emanate from a single, typical stack at the plant center, and the plant could be assumed to have a circular boundary, 200 meters from the plant center. It is anticipated that plant location data (latitude and longitude) will be obtained from EPA permits, and this would allow predicted ambient concentration levels to be compared to potentially-exposed populations through the use of U.S. Census Bureau data. It is also anticipated that more rigorous analyses to provide the distribution of risks among exposed population would be performed where site data are sufficient to support such analyses.

The major influence of the guidelines on exposure assessments is in the quantification of uncertainty. The HEM is being redesigned to explicitly address uncertainty quantitatively where possible. A discussion of risk characterization and attempts to describe and communicate uncertainty was presented previously in Section II.B.4.

TABLE 4 Exposure Modeling Parameters

Modeling Tier	Input Requirements	Output Parameters	Major Assumptions
Tier 1	emission rate, stack height, minimum distance to fenceline	maximum off-site concentrations, worst-case cancer risk or worst-case noncancer hazard index (short- and long-term)	worst-case meteorology, worst-case downwash, worst-case stack parameters, short-term releases occur simultaneously, maximum impacts co-located, cancer risks additive, noncancer risks additive
Tier 2	emission rate, stack height, minimum distance to fenceline, stack velocity, stack temperature, stack diameter, rural/urban site classification, building dimensions for downwash calculation	maximum offsite concentrations, worst-case cancer risk and/or worst-case noncancer hazard index (short- and long-term)	worst-case meteorology, short-term releases occur simultaneously, maximum impacts co-located, cancer risks additive, noncancer risks additive
Tier 3	emission rate, stack height, actual fenceline and release point locations, stack velocity, stack temperature, stack diameter, rural/urban site classification, local meteorological data, receptor locations for concentration predictions, frequency and duration of short-term (intermittent) releases	concentrations at each receptor point, long-term cancer risk estimates, chronic noncancer hazard index estimates at each receptor point, annual hazard index exceedance rate at each receptor	cancer risks additive, noncancer risks additive

III. Question 3: What HAPs data are available now to implement the current risk assessment methodology?

III.A Introduction

The EPA has compiled currently available data on the hazardous air pollutants (HAPs) in developing strategies for implementing various provisions contained in Title III of the Clean Air Act. These data include: information on the schedule for control technology-based standards, recent annual air emissions data, preliminary estimates of the number of facilities that emit HAPs, and health effects information.

III.B Summaries of Available Data

Table 5 is an summary of the currently available health data (this is an updated version of the Table previously provided), taken from Table 6.

TABLE 5 Summary of Health Effects Data (November 1, 1993)[1]

Status	Cancer	Noncancer
Verified RfC		
On IRIS		40
Not on IRIS		2
Reviewed, not verifiable	58	
WOE and IUR	39	
WOE and OUR	14	
WOE Only	35	
Under review[2]	11	23
No status	87	63
Total HAPs	186	186

[1] Does not include lead, radionuclides, or glycol ethers
[2] Under review by Environmental Criteria and Assessment Office or Human Health Assessment Group for derivation of RfC or URE followed by verification review by RfC/RfD and CRAVE work groups before entering data onto IRIS
RfC: Inhalation reference concentration
WOE: Weight-of-evidence, includes A to D class.
IUR: Inhalation unit risk estimate
OUR: Oral unit risk estimate

TABLE 6 Current Data on the HAPs

CAS #	Chemical Name		MY2	AE4	CA71	TR10	1991 Emis (T/yr) 2	1990 Emis (T/yr) 2	1989 Emis (T/yr) 2	1988 Emis (T/yr) 2
	Column Number	#SC								
79345	1,1,2,2-Tetrachloroethane	2	X			X	32.1	22.3	17.7	22.9
79005	1,1,2-Trichloroethane	2	X			X	263.9	299.4	398.4	870.1
57147	1,1-Dimethyl hydrazine	1	X				0.2	0.2	0.4	2.2
120821	1,2,4-Trichlorobenzene	1	X				204.8	188.4	575.7	760.1
96128	1,2-Dibromo-3-chloropropane						0.1			
122667	1,2-Diphenylhydrazine	1	X							
106887	1,2-Epoxybutane (1,2-Butylene oxide)						29.9	39.7	59.8	54.1
75558	1,2-Propylenimine (2-Methyl aziridine)						0.2	0.3	0.3	0.3
106990	1,3-Butadiene	19	X	X	X	X	1975.2	2518.8	2768.7	3268.4
542756	1,3-Dichloropropene (Telone II)	1	X				10.2	29.7	25.5	26.2
1120714	1,3-Propane sultone									
106467	1,4-Dichlorobenzene(p)	1	X				168.1	409.1	793.6	904.2
123911	1,4-Dioxane (1,4-Diethyleneoxide)	1	X				359.3	299.2	390.1	270.4
540841	2,2,4-Trimethylpentane	3	X	X	X					
1746016	2,3,7,8-Tetrachlorodibenzo-p-dioxin			X	X					
95954	2,4,5-Trichlorophenol	1	X						0.1	
88062	2,4,6-Trichlorophenol							0.0	0.1	0.1
94757	2,4-D, salts,esters (Dichlorophenoxyacetic acid)	1				X	8.1	3.9	3.6	3.5
51285	2,4-Dinitrophenol	1	X				12.1	12.3	6.8	10.4
121142	2,4-Dinitrotoluene	1	X				2.7	28.8	43.6	46.1
95807	2,4-Toluene diamine	1	X				1.9	2.0	2.2	1.5
584849	2,4-Toluene diisocyanate	2	X	X			661.9	28.7	61.3	113.9
53963	2-Acetylaminofluorene									
532274	2-Chloroacetophenone	1	X							
79469	2-Nitropropane	1	X				52.9	42.1	112.6	418.6
119904	3,3'-Dimethoxybenzidine							0.0	0.3	
119937	3,3'-Dimethyl benzidine	1	X							
91941	3,3-Dichlorobenzidine							0.0	0.1	0.1
101779	4,4'-Methylenedianiline	1	X				6.6	9.8	23.9	75.1
101144	4,4-Methylene bis(2-chloroaniline)	1	X				0.7	1.4	0.6	0.4
534521	4,6-Dinitro-o-cresol, and salts							0.0	0.1	
92671	4-Aminobiphenyl									
92933	4-Nitrobiphenyl									
100027	4-Nitrophenol	1	X				4.8	3.8	3.9	3.9
75070	Acetaldehyde	8	X	X	X	X	3540.5	3440.3	3762.1	3336.
60355	Acetamide	1	X					0.0		
75058	Acetonitrile	1	X				683.9	831.8	693.4	1022.
98862	Acetophenone	1	X							
107028	Acrolein	7	X		X		14.2	11.0	2.2	16.8
79061	Acrylamide	2	X		X		32.1	25.0	12.5	13.1
79107	Acrylic acid	2	X	X			205.3	213.5	178.7	399.3
107131	Acrylonitrile	7	X	X	X	X	1094.4	1574.0	2191.9	2111.
107051	Allyl chloride	1	X				90.1	103.0	87.8	73.2
62533	Aniline	2	X		X		313.5	237.4	252.1	357.2
0	Antimony Compounds	3			X	X	43.1	73.0	79.3	78.8
0	Arsenic Compounds (inorganic including arsine)	11			X	X	95.2	82.9	87.9	156.7

	IUR per ug/m3	OUR per ug/L	EPA WOE	RfC mg/m3 Stat	IARC WOE	Exp. Asses.	Genetic MVV So	G	Toxicity MVT M	C	Data NM S	E	Repr/ Dev Data
	5	6	7	8	9	10	11		12		13		14
345	5.8E-5	5.8E-6	C		3						+		X
005	1.6E-5	1.6E-6	C	NV	3						-		
147			UR	NV	2B								
0821			D	2.0E-1			+				-		X
128		4.0E-5	B2	2.0E-4	2B			+-		+	+	+	X*
2667	2.2E-4	2.2E-5	B2	NV							+	-	
6887				2.0E-2					+	+	+		
558				NV	2B								
6990	2.8E-4		B2		2B	B	+				+		X
2756			B2	2.0E-2	2B						+		X
20714					2B								
6467				8.0E-1	2B						-		
3911		3.1E-7	B2		1B					-	-		
0841				NV									
46016					2B		-		+		-		X*
954				NV							-		
062	3.1E-6	3.1E-7	B2	NV	2B				+	-	-		
757					2B		-	-	+	+	-		X*
285				NV							-	+	
1142		1.9E-5	B2	NV			-	-	+-		+	-	X*
807				NV	2B								
4849				V	2B						-		
963											+	+	
2274				3.0E-5									
469				2.0E-2	2B								
9904					2B						+		
9937				NV	2B								
941		1.3E-5	B2	NV	2B						+		
01779				UR	2B						+		
01144				NV	2A								
4521				NV									
671					1			+	+		+	+	
933					3								
00027				NV									X
5070	2.2E-6		B2	9.0E-3	2B			+		+	+	+	X
0355					2B								
5058				UR									X
3862			D	NV									
07028			C	2.0E-5	3			-		+	+		X
9061	1.3E-3	1.3E-4	B2	NV	2B		-	+			-		
9107				3.0E-4	3								X
07131	6.8E-5	1.5E-5	B1	2.0E-3	2A	B	-	-	+	+-	+	+	X
07051			C	1.0E-3	3						+		X
2533		1.6E-7	B2	1.0E-3	3		-		+	+	-	-	
	4.3E-3		A	5.0E-5	1	A	+	-	-	+	-	-	

CAS #	Chemical Name		MY 2	AE 4	CA 71	TR 10	1991 Emis (T/yr) 2	1990 Emis (T/yr) 2	1989 Emis (T/yr) 2	1988 Emis (T/yr) 2
	Column Number									
		#SC								
1332214	Asbestos	A*					6.3	8.7	18.7	23.8
71432	Benzene	28	X	X	X	X	8737.2	12203.4	12341.5	14144
92875	Benzidine	1			X					
98077	Benzotrichloride	1	X				3.9	4.2	12.6	12.5
100447	Benzyl chloride	3	X		X	X	13.4	16.8	13.6	21.7
0	Beryllium Compounds	3				X	0.1	0.1	1.7	2.3
57578	beta-Propiolactone	2	X		X					
92524	Biphenyl	3	X		X	X	430.2	560.5	544.1	604.3
111444	Bis(2-chloroethyl)ether (Dichloroethyl ether)	1	X				1.8	1.9	2.4	2.5
117817	Bis(2-ethylhexyl)phthalate (DEHP)						521.7	672.3	539.4	563.9
542881	Bis(chloromethyl)ether	1	X				0.3	0.0		
75252	Bromoform	1	X				0.1	24.1		
0	Cadmium Compounds	16		X	X	X	34.7	45.0	59.9	64.8
156627	Calcium cyanamide						6.3	6.3	6.3	6.3
105602	Caprolactam	4	X		X	X				
133062	Captan						3.6	9.6	12.6	7.9
63252	Carbaryl	1	X				3.4	4.6	5.1	3.7
75150	Carbon disulfide	5	X		X	X	44669.6	49111.3	49897.7	6259(
56235	Carbon tetrachloride	11	X	X	X	X	773.4	835.5	1683.6	1882.
463581	Carbonyl sulfide	3			X	X	8362.6	9317.4	9842.5	8994.
120809	Catechol						2.9	13.9	2.1	1.8
133904	Chloramben							0.0		
57749	Chlordane						0.7	2.2	1.9	0.3
7782505	Chlorine	11			X	X	38804.7	52458.9	66174.1	6674
79118	Chloroacetic acid	3	X		X	X	256.8	12.7	12.4	13.1
108907	Chlorobenzene	3	X		X	X	1198.1	2023.4	2025.4	1965.
510156	Chlorobenzilate									
67663	Chloroform	6	X	X	X	X	9541.4	10881.2	12134.1	1126
107302	Chloromethyl methyl ether						1.7	0.1	0.1	0.1
126998	Chloroprene (2-chloro-1,3-butadiene)	2	X	X			735.3	780.5	503.2	609.1
0	Chromium Compounds (+6 FOR IRIS)	31		X	X	X	278.2	384.8	1119.2	603.9
0	Cobalt Compounds	3			X		16.9	25.9	60.8	43.1
0	Coke Oven Emissions	2		X		X				
1319773	Cresols/Cresylic acid (isomers and mixture)	4	X	X		X	370.7	366.3	446.9	333.(
98828	Cumene (Isopropylbenzene)	3	X	X		X	1638.8	2051.6	2197.5	2359.
0	Cyanide Compounds	7	X	X	X		385.1	569.1	274.5	317.5
72559	DDE (p,p'-Dichlorodiphenyl-dichloroethylene)									
334883	Diazomethane									
132649	Dibenzofuran						20.1	15.1	31.9	35.4
84742	Dibutylphthalate	3		X	X	X	75.1	54.1	116.1	107.8
62737	Dichlorvos						0.3	0.7	0.7	0.5
111422	Diethanolamine	1	X				135.5	191.8	242.1	314.1
64675	Diethyl sulfate	1	X				2.1	2.7	4.4	3.1
60117	Dimethyl aminoazobenzene									
79447	Dimethyl carbamoyl chloride									
68122	Dimethyl formamide	2	X			X				
131113	Dimethyl phthalate	2	X			X	32.9	166.8	181.7	110.8
77781	Dimethyl sulfate	1	X				5.1	4.9	8.2	5.4

	IUR per ug/m3 5	OUR per ug/L 6	EPA WOE 7	RfC mg/m3 Stat 8	IARC WOE 9	Exp. Asses. 10	Genetic MVV So G 11	Toxicity MVT M C 12	Data NM S E 13	Repr/ Dev Data 14
-										
.332214	2.3E-1	Fib/ML	A		1	A	-	-+ +-	- -	
'1432	8.3E-6	8.3E-7	A	UR	1	A	+-	-+ -	- -	X*
)2875	6.7E-2	6.7E-3	A	NV	1		+-	+- +	+ -	
)8077		3.6E-4	B2						+ +	
100447		4.9E-6	B2	NV			-	+- +-	+ +	
)	2.4E-3	1.2E-4	B2	UR	2A	A		+ +	- +	
57578				NV	2B					
)2524			D	NV						
	2.5	3.3E-4	3.3E-5	B2	NV	3		-		+
111444	3.3E-4	3.3E-5	B2	NV	3		-		+	X
117817		4.0E-7	B2		2		- +	- -	- -	X
542881	6.2E-2	6.2E-3	A	NV	1				+	X
75252	1.1E-6	2.3E-7	B2					-	-	
0	1.8E-3		B1	UR	2A	B	- -	+ +-	+	
156627										
105602					4			- -+	-	X
133062			UR	NV	3					
63252				NV	3					
75150				UR			+ +		-	X*
56235	1.5E-5	3.7E-6	B2		2B	B	-		- +	X
463581				NV						
120809					3					
133904										
57749	3.7E-4	3.7E-5	B2	UR	3		-	-+	-	
7782505			D							
79118										
108907			D	UR		B	+	+ -	-	X
510156				NV	3					
67663	2.3E-5	1.7E-7	B2	UR	2B	B	-	- -	- -	X
107302			A	NV	1				+	
126998				7.0E-3	3	B	+ +	-	+	X*
0	1.2E-2		A	UR	1	B	+ +	+ +	+ +	
0									+	
0	6.2E-4		A		1	A				
1319773				NV						
98828				UR						
0			D	V						
72559			9.7E-6	B2				+ +	- -	
334883				NV	3					
132649			D	NV						
84742			D	NV				+	+	X
62737		8.3E-6	C	5.0E-4	3					X
111422										
64675				NV	2A		+	+ +	+ +	
60117										
79447				NV	2A		+	+ -+	+	
68122				3.0E-2			-	-+ -	-	X
131113			D	NV				-	-	
77781			B2	NV	2A		+ +	+ +	+ +	

CAS #	Chemical Name		MY 2	AE 4	CA 71	TR 10	1991 Emis (T/yr) 2	1990 Emis (T/yr) 2	1989 Emis (T/yr) 2	1988 Emis (T/yr) 2
	Column Number	#SC								
106898	Epichlorohydrin (1-chloro-2,3-epoxypropane)	4	X	X			229.6	213.7	234.1	195.1
140885	Ethyl acrylate	3	X	X	X		115.9	102.1	85.6	125.4
100414	Ethyl benzene	23	X	X	X	X	4320.5	4308.8	4270.2	3358.5
51796	Ethyl carbamate (Urethane)						9.9	2.0	1.7	72.7
75003	Ethyl chloride (Chloroethane)	4	X		X	X	1431.6	1971.0	2394.1	2310.5
106934	Ethylene dibromide (Dibromoethane)	1	X				19.1	29.0	29.6	31.7
107062	Ethylene dichloride (1,2-Dichloroethane)	4	X	X	X	X	1997.7	2798.0	2055.1	2383.7
151564	Ethylene imine (Aziridine)								0.3	0.3
75218	Ethylene oxide	4	X	X	X		896.5	1223.7	1514.5	2300.1
96457	Ethylene thiourea						0.3	0.0	0.4	0.3
75343	Ethylidene dichloride (1,1-Dichloroethane)	6	X		X	X				
107211	Et-hylene glycol	3	X	X			5330.1	4694.4	6446.1	6640.3
0	Fine mineral fibers	1				X				
50000	Formaldehyde	22	X	X	X	X	5109.2	6383.0	6281.1	6199.7
0	Glycol ethers	2	X	X			21957.1	24429.1	24238.7	24206.
76448	Heptachlor							0.4	1.7	24.5
118741	Hexachlorobenzene	1	X				0.4	0.7	2.3	2.5
87683	Hexachlorobutadiene	1	X				1.7	2.5	1.8	1.3
77474	Hexachlorocyclopentadiene						12.7	42.3	44.6	7.4
67721	Hexachloroethane	1	X				11.3	4.0	8.5	9.6
822060	Hexamethylene-1,6-diisocyanate									
680319	Hexamethylphosphoramide									
110543	Hexane	20	X	X	X	X				
302012	Hydrazine	1				X	14.2	13.9	15.1	13.9
7647010	Hydrochloric acid	7		X	X	X	41460.7	36723.5	30371.2	36965.
7664393	Hydrogen fluoride (Hydrofluoric acid)	7	X	X	X	X	4590.6	4273.0	4990.1	6054.5
123319	Hydroquinone	4	X		X	X	5.4	5.7	6.4	5.1
78591	Isophorone	1	X							
0	Lead Compounds	22		X	X	X	703.8	812.2	1224.9	1339.7
58899	Lindane (gamma-hexachlorocyclohexane)						0.3	0.8	0.4	0.1
108316	Maleic anhydride	3	X		X	X	229.5	246.5	225.3	382.1
0	Manganese Compounds	19		X	X	X	623.2	1126.4	2215.4	1582.8
0	Mercury Compounds (IRIS-INORGANIC)	11		X	X	X	1.4	0.6	14.6	12.9
67561	Methanol	6	X	X	X		99841.5	100706.2	105913.5	1088
72435	Methoxychlor						0.3	0.8	0.3	136.4
74839	Methyl bromide (Bromomethane)	1	X				1222.8	1102.9	1289.8	595.8
74873	Methyl chloride (Chloromethane)	10	X	X	X	X	2849.4	3821.9	4437.4	4693.3
71556	Methyl chloroform (1,1,1-Trichloroethane)	4	X	X	X	X	68753.1	80699.8	84309.1	83541
78933	Methyl ethyl ketone (2-Butanone)	20	X	X	X	X	51710.9	60663.5	63815.9	62766
60344	Methyl hydrazine	1	X							
74884	Methyl iodide (Iodomethane)						12.7	14.9	12.7	4.5
108101	Methyl isobutyl ketone (Hexone)	14	X	X	X	X	13599.3	13655.7	15341.4	15521
624839	Methyl isocyanate	1	X				3.9	7.2	7.5	5.1
80626	Methyl methacrylate	5	X	X	X		1278.7	1058.1	1571.9	1700.
1634044	Methyl tert butyl ether	1	X				1519.1	1392.3	1495.1	1384.
75092	Methylene chloride (Dichloromethane)	9	X	X	X		39669.2	46248.6	54636.1	60653
101688	Methylene diphenyl diisocyanate (MDI)	1	X				313.2	338.2	312.8	143.3

	IUR per ug/m3 5	OUR per ug/L 6	EPA WOE 7	RfC mg/m3 Stat 8	IARC WOE 9	Exp. Asses. 10	Genetic MVV So G 11	Toxicity MVT M C 12	Data NM S E 13	Repr/ Dev Data 14
106898	1.2E-6	2.8E-7	B2	1.0E-3	2A	B	-+ -	+- +	+ +	X
140885			UR		2B		+	+	-	X
100414			D	1.0E+0			-	+	-	X
51796				NV	2B					
75003				1.3E+1						X
106934	2.2E-4	2.5E-3	B2	2.0E-4	2A		- -	+ +	+ +	X*
107062	2.6E-5	2.6E-6	B2		2B	B	- -	+	+ -	X
151564				NV	3					
75218					2A		+ +	+ +	+ +	X
96457					2B	B	- -	- -	+ +	
75343			C	UR						
107211										
0										
50000	1.3E-5		B1		2A		-+ -	+ +	+ +	X*
0										
76448	1.3E-3	1.3E-4	B2				-	-	+	
118741	4.6E-4	4.6E-5	B2	NV	2B		-	-	-	
87683	2.2E-5	2.2E-6	C		3			-	-	X
77474			D			B				
67721	4.0E-6	4.0E-7	C	NV	3				-	X
822060				1.0E-5	2B					X
680319				7.0E-6	2B					
110543			UR	2.0E-1						X
302012	4.9E-3	8.5E-5	B2		2B		-	-	+ +	
7647010				7.0E-3						X
7664393				UR						
123319				NV	3					
78591		2.7E-8	C	NV					-	X
0			B2		2B		+-	-+	- -	
58899				NV	2B					X*
108316										
0			D	4.0E-4		B			+ +	
0			D	3.0E-4						
57561				UR						X
72435			D	NV	3					
74839			D	5.0E-3	3		+	+	+ +	X
74873				UR	3	B	+	+	+	X
71556			D	UR	3	B				X
78933			D	1.0E+0						X
50344				7.0E-5						
74884				1.0E-2	3		+	+	-	
108101				UR						X
524839				NV						X*
80626					3					X
1634044				5.0E-1	3					X
75092	4.7E-7	2.1E-7	B2	UR	2B		-	- +	+	X
101688				5.0E-5						

CAS #	Chemical Name / Column Number	#SC	MY 2	AE 4	CA 7 1	TR 10	1991 Emis (T/yr) 2	1990 Emis (T/yr) 2	1989 Emis (T/yr) 2	1988 Emis (T/yr) 2
108394	m-Cresol	1	X				38.9	3.8	6.3	9.2
108383	m-Xylene	6	X		X		718.1	601.1	583.7	1012.1
121697	N,N-Dimethyl aniline	1	X				25.6	25.4	45.9	49.5
91203	Naphthalene	2	X	X			1335.9	1853.1	1656.9	1932.1
0	Nickel Compounds (subsulfide)	16		X	X	X	121.6	132.8	466.5	284.1
98953	Nitrobenzene	1	X				26.3	33.1	19.4	19.6
62759	N-Nitrosodimethylamine	1			X					
59892	N-Nitrosomorpholine									
684935	N-Nitroso-N-methylurea									
90040	o-Anisidine	1	X				0.5	0.9	1.1	1.1
95487	o-Cresol	1	X				30.6	19.6	29.8	44.5
95534	o-Toluidine	1	X				5.4	3.7	12.8	23.5
95476	o-Xylene	23	X	X	X	X	864.9	952.3	899.6	979.6
56382	Parathion						0.3	0.3	0.8	1.6
82688	Pentachloronitrobenzene (Quintobenzene)						0.1	0.1	1.1	0.5
87865	Pentachlorophenol	4	X		X	X	6.2	11.6	5.6	7.1
108952	Phenol	12	X	X	X	X	3165.6	3827.4	5264.1	5083.3
75445	Phosgene	2	X		X		2.2	2.4	4.1	10.8
7803512	Phosphine									
7723140	Phosphorus	5		X	X	X	11.7	12.1	30.1	9.6
85449	Phthalic anhydride	5	X		X	X	315.9	343.7	325.1	273.6
1336363	Polychlorinated biphenyls (PCB's)							0.0		0.1
0	Polycylic Organic Matter	12		X	X	X				
123386	Propionaldehyde	4	X			X	694.1	494.5	453.8	523.1
114261	Propoxur (Baygon)							0.1	0.3	0.1
78875	Propylene dichloride (1,2-Dichloropropane)	1	X				386.7	315.3	616.7	682.1
75569	Propylene oxide	16	X	X	X		533.3	680.0	897.1	1482.8
106445	p-Cresol	1	X				67.8	119.5	127.4	320.4
106503	p-Phenylenediamine	1	X				1.8	0.4	2.1	56.9
106423	p-Xylene	3	X		X		2639.2	2969.3	2360.1	3153.3
91225	Quinoline						22.5	13.8	31.8	24.7
106514	Quinone (1,4-benzoquinone)	1	X				2.1	0.8	0.9	5.7
0	Radionuclides (including radon)									
0	Selenium Compounds	15		X	X	X	18.5	15.3	16.7	14.8
100425	Styrene	15	X	X	X	X	14238.2	15838.3	16650.9	17386
96093	Styrene oxide	1	X				0.8	1.2	0.4	1.2
127184	Tetrachloroethylene (Perchloroethylene)	11	X	X	X	X	8343.7	10822.5	12752.4	15794
7550450	Titanium tetrachloride						16.8	27.2	28.6	39.3
108883	Toluene	39	X	X	X	X	99260.1	116912.8	127718.9	135
8001352	Toxaphene (chlorinated camphene)									
79016	Trichloroethylene	8	X	X	X	X	17529.2	18949.0	22162.8	24092
121448	Triethylamine	1	X							
1582098	Trifluralin						5.6	7.8	2.1	1.6
108054	Vinyl acetate	5	X		X		2743.2	2778.4	2699.1	2869.4
593602	Vinyl bromide (bromoethene)						1.8	5.1	0.4	2.5
75014	Vinyl chloride	4	X		X	X	523.7	567.9	634.4	687.2
75354	Vinylidene chloride (1,1-Dichloroethylene)	3	X			X	142.6	151.8	110.3	149.7
1330207	Xylenes (isomers and mixture)	23	X	X	X	X	57776.5	69988.4	73743.4	71332
		Total Emis							708443.8	

	IUR per ug/m3 5	OUR per ug/L 6	EPA WOE 7	RfC mg/m3 Stat 8	IARC WOE 9	Exp. Asses. 10	Genetic MVV So G 11	Toxicity MVT M C 12	Data NM S E 13	Repr/ Dev Data 14
108394			C	NV						
108383				NV			-		-	X
121697										
91?03	4.2E-6		C				-		-	
0	4.8E-4		A	UR	1	B	+ -	-+ +	+ -	
98953			D	UR			-		-	X
62759	1.4E-2	1.4E-3	B2		2A		-	+ +	+ +	
59892					2B					
684935			B2							
90040				NV	2B					
95487			C	NV						
95534					2B		-	+- +-	- -	
95476				NV			-		-	X
56382			C		3					
82688			UR		3					
87865		3.0E-6	B2	UR	2B			- +	-	
108952			D	NV		B	-	+	v	
75445				NV						
7803512			D							
7723140			D							
85449										
1336363		2.2E-4	B2		2A		- -	-	-	X
0			UR			B				
123386				NV						
114261			UR							
78875			UR	6.0E-3	3					X
75569	3.7E-6	6.8E-6	B2	3.0E-2	2A		+ -	+ +	+ +	
106445			C	NV						
106503					3					
106423				NV			-		-	X
91225				NV						
106514				NV						
0			UR			A				
0			D		3					
100425			UR	1.0E+0	2B		+-	+	+	X*
96093					2A		- -	+ +	+ +	X
127184					2B	B	-	+	- -	X
7550450										
108883			D	4.0E-1		B	+	-	-	X*
8001352	3.2E-4	3.2E-5	B2		2B		-		+	
79016			UR	UR	3	B	+ -	+- +-	+ +	X
121448				7.0E-3						
1582098		2.2E-7	C							
108054			UR	2.0E-1	3			+	-	X
593602				3.0E-3	2A				+	
75014	8.4E-5	5.4E-5	A		1	A	+ -	+	+ +	X*
75354	5.0E-5	1.7E-5	C	UR	3	B	- -	- -	+ +	X
1330207			D	NV			-	-	- -	X
	800960.9		863337.1		906614.9		39.0 44.0			

Column Numbers and Footnotes to Table

1 Chemicals emitted from sources that will be regulated within the 2, 4, 7, and 10 year deadlines for maximum achievable control technology standards (# preceding X indicates the # of source categories (#SC) HAP in).

2 Toxic Release Inventory Data (TRI) in tons/year (1988,1989,1990,1991)

5 IUR= Inhalation unit risk estimate per ug/m3; Source is EPA's Integrated Risk Information System (IRIS)

6 OUR= Oral unit risk estimate per ug/l; Source is EPA's IRIS data base

7 WOE= Weight of Evidence classification; Source is EPA's IRIS data base

8 RfC workgroup; verified, on IRIS= conc. given in mg/m3
verified, not on IRIS= 'v'

9 IARC (International Agency for Research on Cancer) WOE

10 Exposure Assessments:
A) HAPS with risk assessments done for development of Section 112 standards
B) HAPS with screening assessments done for listing purposes

11, 12, 13 Information on Genetic Toxicology; Source= Genetic Activity Profiles data base provided by Dr. Michael Waters, EPA's Health Effects Research Lab. (Data as of 1992)
The + or - represents the overall call for that group which may contain more than one assay. When discrepancies exist within a group, this is indicated by a +- (or-+).
The first symbol represents the majority call for that group.

MVV= Mammalian, In Vivo
So= Somatic cell; G= Germ cell
MVT= Mammalian, In Vitro
M= Mutation; C= Chromosome aberration
NM= Non-mammalian
S= Salmonella typhi.; E= Eschericia coli

14 Data from Non-cancer Health Effects Database, prepared and provided by Dr. John Vandenberg, EPA's Health Effects Research Lab.
'X' indicates data available; X* indicates some human data available
Note: Data includes effects on maternal toxicity: All data from Inhalation exposure

Symbols used: UR= under review
V= verified
NA= not available
NV= not verifiable

IARC vs. EPA: Classification Differences

EPA Modifications to IARC Approach:
1. Considers statistically significant association between an agent and life-threatening benign tumors when evaluation human risk
2. Added "no data available" category
3. Added "no evidence of carcinogenicity" category

By Category

EPA

Group A - Known human carcinogen
Group B - Probable human carcinogen
B1 - Limited human data
B2 - Inadequate human data, sufficient animal data
Group C - Possible human carcinogen

IARC

Group 1 - Known human carcinogen
Group 2A - Probable human carcinogen
Group 2B - Possible human carcinogen
Group 3 - Not classifiable as to human carcinogenicity
Group 4 - Probably not carcinogenic to humans

IV. Question 4: What does EPA consider to be the prioritization of the information gathering needs? What criteria would EPA use for determining this prioritization?

IV.A Introduction

Existing data on effects and exposure to the hazardous air pollutants (HAPs) listed under Section 112 have supported a variety of decisions under Title III of the Clean Air Act (CAA). Rules that use these data and additional data collected in a timely fashion will continue to be issued on CAA schedules that extend to the year 2010. Future information gathering on the HAPs will support residual risk decisions, biennial Great Waters reports, urban air toxics reports, and other continuous activities required to administer Section 112 provisions. Interest in the HAPs exists beyond the CAA. Other EPA-administered programs and programs of other agencies address many of the same chemicals and mixtures. Therefore, whatever data are gathered will be gathered with an eye to serving needs beyond Section 112.

The process of prioritizing data collection activities must consider many factors. Decisions for gathering information will have both science and management components. Important considerations include: the types of information needed to make a statutory finding, the current state-of-the-science, priorities given other EPA work, budget constraints, and statutory deadlines. The EPA has not, as yet, made decisions about the extent, mechanism, or timing of data gathering activities. The information presented below generally describes EPA's initial thoughts regarding the gathering of information needed to effectively implement Title III of the CAA.

Under Title IX of the CAA, EPA and other agencies will be looking generally at the research needs for all of the HAPs. This Title provides a forum for planning research to advance the state of the art beyond standard testing. The plans for carrying out this Title are currently being formulated as the Title was added after the FY91 appropriation process was completed.

Overall, the goals by which the priorities and needs can be balanced may be stated as:

- ensure that the data collected meet the requirements of the statutory finding (s) that must be made
- ensure that the data are collected in a timely fashion
- ensure efficient use of resources, given the parallel data gathering efforts of others

- ensure that adequate resources are invested in HAPs that are emitted in significant volumes
- avoid enriching an already rich data base of one HAP at the expense of another HAP of importance

IV.B Criteria for Effects Data-Gathering Plan

The major focus in planning for health and environmental effects data collection activities is to ensure that adequate data are available to conduct the residual risk determinations that will be made under Section 112(f). In order to obtain the data necessary to support these decisions required later in the decade, EPA must begin collection efforts immediately. The Agency anticipates that activities will begin with a ranking of HAPs that takes several factors into account. These factors include:

- promulgation dates of control technology standards
- estimation of the extent to which a particular HAP will contribute to risks resulting from combined HAP emissions from sources in a source category (using effects and exposure data available now)
- importance of a HAP to the Great Waters or Urban Area Source programs
- overlapping priority/interest of other EPA programs or governmental agencies (e.g. timing of ongoing Agency for Toxic Substances and Disease Registry or National Toxicology Program activities)

Decisions on the extent and type of data to be gathered on potential adverse effects associated with exposure to a HAP will also require a balancing of several factors including incorporation of professional judgment on the likelihood that additional data may significantly alter current opinions on the toxicity of a specific HAP. Critical elements will include:

- the richness of the current data base
- the need for data to enable route-to-route extrapolation of existing toxicity data
- the need to expand a data set on an already identified endpoint in order to improve dose-response characterization
- the need to extend the scope of data to cover endpoints other than those previously identified
- the need for research beyond standard test protocols to understand biological fate and transformation or mechanism of action

IV.C Options for Scope of Effects Data-gathering

While the alternatives have not been exhaustively explored, and substantial work remains to be done, there are three general options that are being considered. These options are:

1. Board Scope. This approach would use staged testing for a large number of HAPs, screening a range of endpoints and proceeding to full endpoint tests as the screening assays indicate.
2. Medium Scope. This option would focus screening tests on those HAPs with the most significant emissions. Testing strategies would be more robust and address critical endpoints (carcinogenicity and developmental toxicity, at a minimum). Other HAPs with significant emissions would be considered under the narrow scope testing identified below.
3. Narrow Scope. Under this alternative, testing would focus on complimenting and making more useable existing data bases. For example, HAPs with significant emissions may be studied to "convert" oral to inhalation data or to elucidate dose-response relationships. This narrow scope testing could include: pharmacokinetics studies, a 90 day subchronic inhalation study, or a repeat of a previous study on an endpoint to better define the dose-response relationship.

IV.D Mechanisms for Obtaining Effects Data

There are a variety of mechanisms that may be accessed for collecting effects data, all of which will likely be employed. Major data gathering efforts are underway that will complement data collected specifically for Section 112 use. For example, the Superfund Amendments and Reauthorization Act of 1986 (SARA) requires the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicity profiles for over 200 pollutants. These profiles identify data gaps and efforts will be put forth to fill these gaps. Of the pollutants studied by ATSDR, 76 are HAPs. A second example is efforts being undertaken by the European communities. They are interested in generating data for a list of chemicals that overlaps the HAPs list. In addition, the National Toxicology Program (NTP) is working with EPA to identify testing and research the NTP can undertake for several HAPs. The EPA's Health and Environmental Research Laboratory (HERL) has ongoing research that addresses several HAPs, as well as urban toxics issues. This laboratory also conducts fundamental research on pharmacokinetics applicable to the HAPs. Additional EPA laboratories are conducting research on environmental fate, ecological effects, etc. Another alternative for collecting data is to access the regulatory test program under the Toxic Substances

Control Act (TSCA) to require that industry conduct testing. Finally, the CAA Title IX research program will be pursued for research on HAPs. Making these overlapping efforts work together will be part of any data gathering EPA does on the HAPs.

IV.E Improving Data Bases for Estimating Exposure to HAPs

In addition to developing quantitative relationships between HAP concentrations and health or environmental effects, it is critical that the EPA pursue parallel efforts to support accurate characterization of the levels of exposure associated with sources of the HAPs. In the past, efforts to obtain sufficient information to accurately characterize HAP exposure levels in the vicinity of an industrial source have focused on one pollutant at a time. These efforts have been severely limited by lack of information on the source(s) being evaluated. In lieu of site-specific data for exposure characterization, EPA has settled for "model plant" types of analyses, which rely on only a sampling of data from one type of source and extrapolate exposure estimates to the rest of the source population. These analyses by nature must be very conservative, and therefore tend to overestimate ambient exposure levels due to any one type of industrial source. As a result, these analyses are often criticized by industry as being "overly conservative".

It is clear that the CAA mandate for residual risk analyses (after the implementation of MACT) would require that such analyses be based on site-specific data rather than "model plant" scenarios. These analyses must therefore require more site-specific data than are currently available. In addition, the analyses will differ from past analyses in that they will be directed at assessing the exposure to multiple pollutants being emitted from a source in a particular source category. The EPA must begin now to develop the tools and process for obtaining the necessary data to perform residual risk analyses. While such efforts may build on past efforts, there are several new and challenging aspects that must be addressed, including:

1) Emission levels of each of the HAPs from each source within a source category must be obtained. Since EPA-approved measurement methods are not available for all HAPs, this will entail research and development efforts for both measurement methods and site-specific emission estimation techniques. It is hoped that cooperative efforts can be undertaken with industry to expand the publicly-available expertise in this area.
2) Data are to be obtained on a source category-by-source category basis. Since most currently available data bases are on a pollutant-by-pollutant basis, most of the current data will be inadequate for this purpose.

3) Exact stack, vent, and fugitive emission locations as well as fenceline locations for each facility are crucial for reducing the uncertainty of exposure assessments. Very little data are available in this regard, and it is unclear whether most industries will be willing to provide such data.
4) Development of guidelines is needed to explore the use of monitoring data or other more direct measures of exposure in assessing exposures resulting from emissions of HAPS. Specifically, the use of these data to complement modeling analyses needs to be examined.
5) Development of a user-friendly, easy-access, centralized data base and retrieval system (such as an electronic bulletin board system) may be desirable to provide a convenient vehicle for obtaining the necessary data. Industry input and cooperation in such development would be crucial to its success. Making sure that industry realizes that, without the necessary data, EPA efforts to assess exposure will be "conservative", may provide the needed cooperation of industry. Development of a data base system that is easy to use will substantially reduce the burden on industry as well as reduce the paperwork that would otherwise be necessary for such an information request.
6) Efforts to check and assure the quality of the data obtained for exposure assessments may prove to be a large part of the data gathering process.
7) Efforts to appropriately include population mobility and microenvironment exposures into the overall exposure assessment process have already begun. Sensitivity studies are needed, however, to determine the extent to which such factors can affect the overall exposure and risk assessment results.
8) Inclusion of short-term exposure quantification is important for many HAPs. Some modeling techniques are already available to address this quantification, but data on short-term emissions variability are generally lacking. The extent to which such information becomes available will dictate the extent to which EPA can incorporate such variability in exposure assessments.
9) Concentration measurements to assist in the validation of human exposure modeling results are generally lacking for most HAPs. While validation of air dispersion models in the field has been done, indoor/outdoor partitioning and multiple route exposures have not received the same level of validation efforts. This is an area where more data would be helpful.

EPA welcomes comments and suggestions from the Committee on the plans for improving the accuracy of exposure and risk assessments required to implement the CAA. Of specific interest are the recommendations of the panel for prioritizing the vast amount of work that is required to fill the existing data gaps.

V. Question 5: What does EPA consider to be some of the critical management aspects of risk assessment decision-making that may not be apparent to an outside observer?

The current regulatory process places a number of challenging demands on the risk manager. Depending on the nature of the regulation and the legislative authority, he or she must try to assimilate a variety of analyses—legal, economic, social and scientific—of which risk characterization is only one part. Because of this diversity, the risk manager must relay on the products of experts in a range of disciplines.

In making risk management decisions, there are a number of considerations and factors to be weighed that may not be apparent to outside observers. Some of the factors influencing these decisions are described below.

1. In dealing with scientific issues, the risk manager is typically a generalist with no particular expertise in the area of risk assessment. This places particular requirements on the risk assessment process. Thus, the products of the risk assessment process must be designed to aid these individuals in decision-making. Risk managers are often frustrated by complex discussions of scientific uncertainties (mechanism of action, uncertainty in extrapolation, etc.). Rather they tend to desire bottom-line characterizations of the likelihood and magnitude of potential problems. In many respects, the popularity of the current cancer classification system lies in its ability to characterize the overall weight of evidence by readily-comprehended categories (e.g., known, probable, possible carcinogen) and the presentation of a measure of carcinogenic potency.

   The Agency has increased the emphasis placed on the risk characterization component of risk assessment, and is moving toward a more comprehensive examination of the assumptions and uncertainties in risk assessment. The fact remains, however, that communication of the critical elements of a risk assessment to risk managers remains a challenge.
2. Consistency is important. This does not mean that all risk assessments should look the same. But it is important that a consistent terminology be adopted, even if the terminology draws controversy, and that the risk managers understand and can communicate that understanding. Decision-makers build on previous decisions and examples to put current issues in context. If formats or meanings differ from case to case, this process becomes difficult, if not impossible.
3. Risk managers do not expect perfect information. Critics of risk assessment's imperfections must recognize that public policy is often a blunt instrument rather than a surgeon's scalpel. Decisions are often based on broad bands

of uncertainty within which even differences of several fold may not affect the decision.

It is important for both risk managers and critics of risk assessment to avoid pursuing the ideal risk assessment. These individuals must bear in mind the limits of the real world. These limits include time, money, and the state of scientific knowledge.

4. Statutory mandates may place constraints on the development and use of risk characterization data that are not consistent with our understanding of the underlying science. The establishment of risk targets (or bright lines) such as 10^{-6}, for example, have been criticized as not allowing the consideration of weight-of-evidence in decision making. Another example is the requirement that the Agency consider the risk to the "person most exposed" to emissions from an air toxics source. Thus, the statutory framework constrains full consideration of the distribution of risk across the exposed population.
5. Statutes or court action often mandate regulation at a specific time, effectively mandating decision-making based upon available data. This is exacerbated by the fact that the development of robust health and safety data (e.g., well-conducted animal bioassays, epidemiological, or exposure studies) are both resource- and time-intensive.
6. The risk management process is often the focus of considerable outside attention and controversy. This is particularly true where the impacts of decisions are costly, or where they adversely affect well-organized groups. On these circumstances, there is a natural tendency to continue the process of data development and analysis, rather than to make decisions in an atmosphere of uncertainty. While such an environment can cause delay, it can also have the effect of encouraging more rigorous examination of data and careful consideration of options.
7. Persistent requests for information and more studies lead to paralysis by analysis and the waste of limited resources. The risk of inaction is often forgotten. Additional information needs must be balanced against the need to take timely action where it is warranted. This is particularly true in the risk assessment process, where the limitations of the current state of the science often prevent definitive answers, and can encourage continual additional data development. Reviewers of Agency risk assessments must consider the reasonable resource constraints under which the Agency operates.

Appendix B

EPA Memorandum from Henry Habicht

MEMORANDUM

SUBJECT: Guidance on Risk Characterization for Risk Managers and Risk Assessors
FROM: F. Henry Habicht II
Deputy Administrator
TO: Assistant Administrators
Regional Administrators

Introduction

This memorandum provides guidance for managers and assessors on describing risk assessment results in EPA reports, presentations, and decision packages. The guidance addresses a problem that affects public perception regarding the reliability of EPA's scientific assessments and related regulatory decisions. EPA has talented scientists, and public confidence in the quality of our scientific output will be enhanced by our visible interaction with peer scientists and through presentation of risk assessments and underlying scientific data.

Specifically, although a great deal of careful analysis and scientific judgment goes into the development of EPA risk assessments, significant information is often omitted as the results of the assessments are passed along in the decision-making process. Often, when risk information is presented to the ultimate decision-maker and to the public, the results have been boiled down to a point estimate of risk. Such "short hand" approaches to risk assessment do not fully convey the range of information considered and used in developing the assessment. In short, informative risk characterization clarifies the scientific

basis for EPA decisions, while numbers alone do not give a true picture of the assessment.

This problem is not EPA's alone. Agency contractors, industry, environmental groups, and other participants in the overall regulatory process use similar "short hand" approaches.

We must do everything we can to ensure that critical information from each stage of the risk assessment is communicated from risk assessors to their managers, from middle to upper management, from EPA to the public, and from others to EPA. The Risk Assessment Council considered this problem over many months and reached several conclusions: 1) We need to present a full and complete picture of risk, including a statement of confidence about data and methods used to develop the assessment; 2) we need to provide a basis for greater consistency and comparability in risk assessment across Agency programs; and 3) professional scientific judgment plays an important role in the overall statement of risk. The Council also concluded that Agency-wide guidance would be useful.

Background

Principles emphasized during Risk Assessment Council discussions are summarized below and detailed in the attached Appendix.

Full Characterization of Risk

EPA decisions are based in part on risk assessment, a technical analysis of scientific information on existing and projected risks to human health and the environment. As practiced at EPA, the risk assessment process depends on many different kinds of scientific data (e.g., exposure, toxicity, epidemiology), all of which are used to "characterize" the expected risk to human health or the environment. Informed use of reliable scientific data from many different sources is a central feature of the risk assessment process.

Highly reliable data are available for many aspects of an assessment. However, scientific uncertainty is a fact of life for the risk assessment process as a whole. As a result, agency managers make decisions using scientific assessments that are less certain than the ideal. The issues, then, become when is scientific confidence sufficient to use the assessment for decision-making, and should the assessment be used? In order to make these decisions, mangers need to understand the strengths and limitations of the assessment.

On this point, the guidance emphasizes that informed EPA risk assessors

and managers need to be completely candid about confidence and uncertainties in describing risks and in explaining regulatory decisions. Specifically, the Agency's risk assessment guidelines call for full and open discussion of uncertainties in the body of each EPA risk assessment, including prominent display of critical uncertainties in the risk characterization. Numerical risk estimates should always be accompanied by descriptive information carefully selected to ensure an objective and balanced characterization of risk in risk assessment reports and regulatory documents.

Scientists call for fully characterizing risk not to question the validity of the assessment, but to fully inform others about critical information in the assessment. The emphasis on "full" and "complete" characterization does not refer to an ideal assessment in which risk is completely defined by fully satisfactory scientific data. Rather, the concept of complete risk characterization means that information that is needed for informed evaluation and use of the assessment is carefully highlighted. Thus, even though risk characterization details limitations in an assessment, a balanced discussion of reliable conclusions and related uncertainties enhances, rather than detracts, from the overall credibility of each assessment.

This guidance is not new. Rather, it re-states, clarifies, and expands upon current risk assessment concepts and practices, and emphasizes aspects of the process that are often incompletely developed. It articulates principles that have long guided experienced risk assessors and well-informed risk managers, who recognize that risk is best described not as a classification or single number, but as a composite of information from many different sources, each with varying degrees of scientific certainty.

Comparability and Consistency

The Council's second finding, on the need for greater comparability, arose for several reasons. One was confusion—for example, many people did not understand that a risk estimate of 10^{-6} for an "average" individual should not be compared to another 10^{-6} risk estimate for the "most exposed individual." Use of such apparently similar estimates without further explanation leads to misunderstandings about the relative significance of risks and the protectiveness of risk reduction actions. Another catalyst for change was the SAB's report, Reducing Risk: Setting Priorities and Strategies for Environmental Protection . In order to implement the SAB's recommendation that we target our efforts to achieve the greatest risk reduction, we need common measurements of risk.

EPA's newly revised Exposure Assessment Guidelines provide standard descriptors of exposure and risk. Use of these terms in all Agency risk assessments

will promote consistency and comparability. Use of several descriptors, rather than a single descriptor, will enable us to present a more complete picture of risk that corresponds to the range of different exposure conditions encountered by various populations exposed to most environmental chemicals.

Professional Judgment

The call for more extensive characterization of risk has obvious limits. For example, the risk characterization includes only the most significant data and uncertainties from the assessment (those that define and explain the main risk conclusions) so that decision-makers and the public are not overwhelmed by valid but secondary information.

The degree to which confidence and uncertainty are addressed depends largely on the scope of the assessment and available resources. When special circumstances (e.g., lack of data, extremely complex situations, resource limitations, statutory deadlines) preclude a full assessment, such circumstances should be explained. For example, an emergency telephone inquiry does not require a full written risk assessment, but the caller must be told that EPA comments are based on a "back-of-the-envelope" calculation and, like other preliminary or simple calculations, cannot be regarded as a risk assessment.

Guidance Principles

Guidance principles for developing, describing, and using EPA risk assessments are set forth in the Appendix. Some of these principles focus on differences between risk assessment and risk management, with emphasis on differences in the information content of each process. Other principles describe information expected in EPA risk assessments to the extent practicable, emphasizing that discussion of both data and confidence in the data are essential features of a complete risk assessment. Comments on each principle appear in the Appendix; more detailed guidance is available in EPA's risk assessment guidelines (e.g., 51 Federal Register 33992-34054, 24 September 1986).

Like the EPA's risk assessment guidelines, this guidance applies to the development, evaluation, and description of Agency risk assessments for use in regulatory decision-making. This memorandum does not give guidance on the use of completed risk assessments for risk management decisions, nor does it address the use of non-scientific considerations (e.g., economic or societal factors) that are considered along with the risk assessment in risk management and decision-making. While some aspects of this guidance focus on cancer risk assessment, the guidance applies generally to human health effects (e.g., neurotoxicity, developmental toxicity) and, with appropriate modifications, should be

used in all health risk assessments. Guidance specifically for ecological risk assessment is under development.

Implementation

Effective immediately, it will be Agency policy for each EPA office to provide several kinds of risk assessment information in connection with new Agency reports, presentation, and decision packages. In general, such information should be presented as carefully selected highlights from the overall assessment. In this regard, common sense regarding information needed to fully inform Agency decision-makers is the best guide for determining the information to be highlighted in decision packages and briefings.

1. Regarding the interface between risk assessment and risk management, risk assessment information must be clearly presented, separate from any non-scientific risk management considerations. Discussion of risk management options should follow, based on consideration of all relevant factors, scientific and non-scientific.
2. Regarding risk characterization, key scientific information on data and methods (e.g., use of animal or human data for extrapolating from high to low doses, use of pharmacokinetics data) must be highlighted. We also expect a statement of confidence in the assessment that identifies all major uncertainties along with comment on their influence on the assessment, consistent with guidance in the attached Appendix.
3. Regarding exposure and risk characterization, it is Agency policy to present information on the range of exposures derived from exposure scenarios and on the use of multiple risk-descriptors (i.e., central tendency, high end of individual risk, population risk, important subgroups, if known) consistent with terminology in the attached Appendix and Agency guidelines.

This guidance applies to all Agency offices. It applies to assessments generated by EPA staff and those generated by contractors for EPA's use. I believe adherence to this Agency-wide guidance will improve understanding of Agency risk assessments, lead to more informed decisions, and heighten the credibility of both assessments and decisions.

From this time forward, presentations, reports, and decision packages from all Agency offices should characterize risk and related uncertainties as described here. Please be prepared to identify and discuss with me any program-specific modifications that may be appropriate. However, we do not expect risk assessment

documents that are close to completion to be rewritten. Although this is internal guidance that applies directly to assessments developed under EPA auspices, I also encourage Agency staff to use these principles as guidance in evaluating assessments submitted to EPA from other sources, and in discussing these submissions with me and with the Administrator.

This guidance is intended for both management and technical staff. Please distribute this document to those who develop or review assessments and to your mangers who use them to implement Agency programs. Also, I encourage you to discuss the principles outlined here with your staff, particularly in briefings on particular assessments.

In addition, I expect that the Risk Assessment Council will endorse new guidance on Agency-wide approaches to risk characterization now being developed in the Risk Assessment Forum for EPA's risk assessment guidelines, and that the Agency and the Council will augment that guidance as needed.

The Administrator and I believe that this effort is very important. It furthers our goals of rigor and candor in the preparation, presentation, and use of EPA risk assessments. The tasks outlined above may require extra effort from you, your managers, and your technical staff, but they are critical to full implementation of these principles. We are most grateful for the hard work of your representatives on the RAC and other staff in pulling this document together. I appreciate your cooperation in this important area of science policy, and look forward to our discussions.

Attachment

cc: The Administrator
Risk Assessment Council

Guidance For Risk Assessment

U.S. Environmental Protection Agency

Risk Assessment Council

November, 1991

Section 1. Risk Assessment — Risk Management Interface

Recognizing that for many people the term risk assessment has wide meaning, the National Research Council's 1983 report on risk assessment in the federal government (hereafter "NRC report") distinguished between risk assessment and risk management.

> Broader uses of the term [risk assessment] than ours also embrace analysis of perceived risks, comparison of risks associated with different regulatory strategies, and occasionally analysis of the economic and social implications of regulatory decisions—functions that we assign to risk management (emphasis added). (1)

In 1984, EPA endorsed these distinctions between risk assessment and risk management for Agency use (2), and later relied on them in developing risk assessment guidelines (3).

This distinction suggests that EPA participants in the process can be grouped into two main categories, each with somewhat different responsibilities, based on their roles with respect to risk assessment and risk management.

Risk Assessment

One group generates the risk assessment by collecting, analyzing, and synthesizing scientific data to produce the hazard identification, dose-response, and exposure assessment portion of the risk assessment and to characterize risk. This group relies in part on Agency risk assessment guidelines to address science policy issues and scientific uncertainties.

Generally, this group includes scientists and statisticians in the Office of Research and Development, the Office of Pesticides and Toxic Substances and other program offices, the Carcinogen Assessment Verification Endeavor (CRAVE), and the RfD/RfC Workgroups.

Others use analyses produced by the first group to generate siteor media-specific exposure assessments and risk characterizations for use in regulation development. These assessors rely on existing databases (e.g., IRIS, ORD Health Assessment Documents, CRAVE, and RfD/RfC Workgroup documents) to develop regulations and evaluate alternatives.

Generally, this group includes scientists and analysts in program offices, regional offices, and the Office of Research and Development.

Risk Management

A third group integrates the risk characterization with other non-scientific

considerations specified in applicable statutes to make and justify regulatory decisions.

Generally, this group includes Agency managers and decision-makers.

Each group has different responsibilities for observing the distinction between risk assessment and risk management. At the same time, the risk assessment process involves regular interaction between each of the groups, with overlapping responsibilities at various stages in the overall process.

The guidance to follow outlines principles specific for those who generate, review, use, and integrate risk assessments for decision-making.

1. Risk assessors and risk managers should be sensitive to distinctions between risk assessment and risk management.

The major participants in the risk assessment process have many shared responsibilities. Where responsibilities differ, it is important that participants confine themselves to tasks in their areas of responsibility and not inadvertently obscure differences between risk assessment and risk management.

Shared responsibilities of assessors and managers include initial decisions regarding the planning and conduct of an assessment, discussions as the assessment develops, decisions regarding new data needed to complete an assessment and to address significant uncertainties. At critical junctures in the assessment, such consultations shape the nature of, and schedule for, the assessment.

For the generators of the assessment, distinguishing between risk assessment and risk management means that scientific information is selected, evaluated, and presented without considering non-scientific factors including how the scientific analysis might influence the regulatory decision. Assessors are charged with (1) generating a credible, objective, realistic, and balanced analysis; (2) presenting information on hazard, dose-response, exposure and risks; and (3) explaining confidence in each assessment by clearly delineating uncertainties and assumptions along with the impacts of these factors (e.g., confidence limits, use of conservative/non-conservative assumptions) on the overall assessment. They do not make decisions on the acceptability of any risk level for protecting public health or selecting procedures for reducing risks.

For users of the assessment and for decision-makers who integrate these assessments into regulatory decisions, the distinction between risk assessment and risk management means refraining from influencing the risk description through consideration of non-scientific factors—e.g., the regulatory outcome—and from attempting to shape the risk assessment to avoid statutory constraints, meet regulatory objectives, or serve political purposes. Such management considerations are often legitimate considerations for the overall regulatory decision (see next principle), but they have no role in estimating or describing risk.

However, decision-makers establish policy directions that determine the

overall nature and tone of Agency risk assessments and, as appropriate, provide policy guidance on difficult and controversial risk assessment issues. Matters such as risk assessment priorities, degree of conservatism, and acceptability of particular risk levels are reserved for decision-makers who are charged with making decisions regarding protection of public health.

2. The risk assessment product, that is, the risk characterization, is only one of several kinds of information used for regulatory decision-making.

Risk characterization, the last step in risk assessment, is the starting point for risk management considerations and the foundation for regulatory decision-making, but it is only one of several important components in such decisions. Each of the environmental laws administered by EPA calls for consideration of non-scientific facts at various stages in the regulatory process. As authorized by different statutes, decision-makers evaluate technical feasibility (e.g., treatability, detection limits), economic, social, political, and legal factors as part of the analysis of whether or not to regulate and; if so, to what extent. Thus, regulatory decisions are usually based on a combination of the technical analysis used to develop the risk assessment and information from other fields.

For this reason, risk assessors and managers should understand that the regulatory decision is usually not determined solely by the outcome of the risk assessment. That is, the analysis of the overall regulatory problem may not be the same as the picture presented by risk analysis alone. For example, a pesticide risk assessment may describe moderate risk to some populations but, if the agricultural benefits of its use are important for the nation's food supply, the product may be allowed to remain on the market with ceratin restrictions on use to reduce possible exposure. Similarly, assessment efforts may produce an RfD for a particular chemical, but other considerations may result in a regulatory level that is more or less protective than the RfD itself.

For decision-makers, this means that societal considerations (e.g., costs, benefits) that, along with the risk assessment, shape the regulatory decision should be described as fully as the scientific information set forth in the risk characterization. Information on data sources and analyses, their strengths and limitations, confidence in the assessment, uncertainties, and alternate analyses are as important here as they are for the scientific components of the regulatory decision. Decision-makers should be able to expect, for example, the same level of rigor from the economic analysis as they receive from the risk analysis.

Decision-makers are not "captive of the numbers." On the contrary, the quantitative and qualitative risk characterization is only one of many important factors that must be considered in reaching the final decision—a difficult and distinctly different task from risk assessment per se. Risk management decisions involve numerous assumptions and uncertainties regarding technology, economics

and social factors, which need to be explicitly identified for the decision-makers and the public.

Section 2. Risk Characterization

EPA risk assessment principles and practices draw on many sources. The environmental laws administered by EPA, the National Research Council's 1983 report on risk assessment (1), the Agency's Risk Assessment Guidelines (3), and various program-specific guidance (e.g., the Risk Assessment Guidance for Superfund) are obvious sources. Twenty years of EPA experience in developing, defending, and enforcing risk assessment-based regulation is another. Together these various sources stress the importance of a clear explanation of Agency processes for evaluating hazard, dose-response, exposure, and other data that provide the scientific foundation for characterizing risk.

This section focuses on two requirements for full characterization of risk. First, the characterization must address qualitative and quantitative features of the assessment. Second, it must identify any important uncertainties in the assessment as part of a discussion on confidence in the assessment.

This emphasis on a full description of all elements of the assessment draws attention to the importance of the qualitative as well as the quantitative dimensions of the assessment. The 1983 NRC report carefully distinguished qualitative risk assessment from quantitative assessments, preferring risk statements that are not strictly numerical.

> The term risk assessment is often given narrower and broader meanings than we have adopted here. For some observers, the term is synonymous with quantitative risk assessment and emphasizes reliance on numerical results. Our broader definition includes quantification, but also includes qualitative expressions of risk. Quantitative estimates of risk are not always feasible, and they may be eschewed by agencies for policy reasons (Emphasis in original) (1)

More recently, an Ad Hoc Study Group (with representatives from EPA, HHS, and the private sector) on Risk Presentation reinforced and expanded upon these principles by specifying several "attributes" for risk characterization.

1. The major components of risk (hazard identification, dose-response, and exposure assessment) are presented in summary statements, along with quantitative estimates of risk, to give a combined and integrated view of the evidence.
2. The report clearly identifies key assumptions, their rationale, and the extent of scientific consensus; the uncertainties thus accepted; and the effect of reasonable alternative assumptions on conclusions and estimates.

3. The report outlines specific ongoing or potential research projects that would probably clarify significantly the extent of uncertainty in the risk estimation.…(4)

Particularly critical to full characterization of risk is a frank and open discussion of the uncertainty in the overall assessment and in each of its components. The uncertainty statement is important for several reasons.

- Information from different sources carries different kinds of uncertainty and knowledge of these differences is important when uncertainties are combined for characterizing risk.
- Decisions must be made on expending resources to acquire additional information to reduce the uncertainties.
- A clear and explicit statement of the implications and limitations of a risk assessment requires a clear and explicit statement of related uncertainties.
- Uncertainty analysis gives the decision-maker a better understanding of the implications and limitations of the assessments.

A discussion of uncertainty requires comment on such issues as the quality and quantity of available data, gaps in the data base for specific chemicals, incomplete understanding of general biological phenomena, and scientific judgments or science policy positions that were employed to bridge information gaps.

In short, broad agreement exists on the importance of a full picture of risk, particularly including a statement of confidence in the assessment and that the uncertainties are within reason. This section discusses information content and uncertainty aspects of risk characterization, while Section 3 discusses various descriptors used in risk characterization.

1. The risk assessment process calls for characterizing risk as a combination of qualitative information, quantitative information, and information regarding uncertainties.

Risk assessment is based on a series of questions that the assessor asks about the data and the implications of the data for human risk. Each question calls for analysis and interpretation of the available studies, selection of the data that are most scientifically reliable and most relevant to the problem at hand, and scientific conclusions regarding the question presented. As suggested below, because the questions and analyses are complex, a complete characterization includes several different kinds of information, carefully selected for reliability and relevance.

a. Hazard identification — What do we know about the capacity of an environmental agent for causing cancer (or other adverse effects) in laboratory animals and in humans?

Hazard identification is a qualitative description based on factors such as the kind and quality of data on humans or laboratory animals, the availability of ancillary information (e.g., structure-activity analysis, genetic toxicity, pharmacokinetics) from other studies, and the weight-of-the evidence from all of these data sources. For example, to develop this description, the issues addressed include:

1. the nature, reliability, and consistency of the particular studies in humans and in laboratory animals;
2. the available information on the mechanistic basis for activity; and
3. experimental animal responses and their relevance to human outcomes.

These issues make clear that the task of hazard identification is characterized by describing the full range of available information and the implications of that information for human health.

b. Dose-Response Assessment — What do we know about the biological mechanisms and dose-response relationships underlying any effects observed in the laboratory or epidemiology studies providing data for the assessment?

The dose-response assessment examines quantitative relationships between exposure (or dose) and effects in the studies used to identify and define effects of concern. This information is later used along with "real world" exposure information (see below) to develop estimates of the likelihood of adverse effects in populations potentially at risk.

Methods for establishing dose-response relationships often depend on various assumptions used in lieu of a complete data base and the method chosen can strongly influence the overall assessment. This relationship means that careful attention to the choice of a high-to-low dose extrapolation procedure is very important. As a result, an assessor who is characterizing a dose-response relationship considers several key issues:

1. relationship between extrapolation models selected and available information on biological mechanisms;
2. how appropriate data sets were selected from those that show the range of possible potencies both in laboratory animals and humans;
3. basis for selecting interspecies dose scaling factors to account for scaling doses from experimental animals to humans; and
4. correspondence between the expected route(s) of exposure and the exposure route(s) utilized in the hazard studies, as well as the interrelationships of potential effects from different exposure routes.

EPA's Integrated Risk Information System (IRIS) is a primary source of this information. IRIS includes data summaries representing Agency consensus on specific chemicals, based on a careful review of the scientific issues listed above.

For specific risk assessments based on data in IRIS and on other sources, risk assessors should carefully review the information presented, emphasizing confidence in the database and uncertainties (see subsection d below). The IRIS statement of confidence should be included as part of the risk characterization for hazard and dose-response information.

c. Exposure Assessment — What do we know about the paths, patterns, and magnitudes of human exposure and numbers of persons likely to be exposed?

The exposure assessment examines a wide range of exposure parameters pertaining to the "real world" environmental scenarios of people who may be exposed to the agents under study. The data considered for the exposure assessment range from monitoring studies of chemical concentrations in environmental media, food, and other materials to information on activity patterns of different population subgroups. An assessor who characterizes exposure should address several issues.

1. The basis for values and input parameters used for each exposure scenario. If based on data, information on the quality, purpose, and representativeness of the database is needed. If based on assumptions, the source and general logic used to develop the assumption (e.g., monitoring, modeling, analogy, professional judgment) should be described.
2. The major factor or factors (e.g., concentration, body uptake, duration/ frequency of exposure) thought to account for the greatest uncertainty in the exposure estimate, due either to sensitivity or lack of data.
3. The link of the exposure information to the risk descriptors discussed in Section 3 of this Appendix. This issue includes the conservatism or non-conservatism of the scenarios, as indicated by the choice of descriptors.

In summary, confidence in the information used to characterize risk is variable, with the result that risk characterization requires a statement regarding the assessor's confidence in each aspect of the assessment.

d. Risk Characterization — What do other assessors, decision-makers, and the public need to know about the primary conclusions and assumptions, and about the balance between confidence and uncertainty in the assessment?

In the risk characterization, conclusions about hazard and dose response are integrated with those from the exposure assessment. In addition, confidence about theses conclusions, including information about the uncertainties associated with the final risk summary, is highlighted. As summarized below, the

characterization integrates all of the preceding information to communicate the overall meaning of, and confidence in, the hazard, exposure, and risk conclusions.

Generally, risk assessments carry two categories of uncertainty, and each merits consideration. Measurement uncertainty refers to the usual variance that accompanies scientific measurements (such as the range around an exposure estimate) and reflects the accumulated variances around the individual measured values used to develop the estimate. A different kind of uncertainty stems from data gaps—that is, information needed to complete the data base for the assessment. Often, the data gap is broad, such as the absence of information on the effects of exposure to a chemical on humans or on the biological mechanism of action of an agent.

The degree to which confidence and uncertainty in each of these areas is addressed depends largely on the scope of the assessment and the resources available. For example, the Agency does not expect an assessment to evaluate and assess every conceivable exposure scenario for every possible pollutant, to examine all susceptible populations potentially at risk, or to characterize every possible environmental scenario to determine the cause and effect relationships between exposure to pollutants and adverse health effects. Rather, the uncertainty analysis should reflect the type and complexity of the risk assessment, with the level of effort for analysis and discussion of uncertainty corresponding to the level of effort for the assessment. Some sources of confidence and of uncertainty are described below.

Often risk assessors and managers simplify discussion of risk issues by speaking only of the numerical components of an assessment. That is, they refer to the weight-of-evidence, unit risk, the risk-specific dose or the q^{1*} for cancer risk, and the RfD/RfC for health effects other than cancer, to the exclusion of other information bearing on the risk case. However, since every assessment carries uncertainties, a simplified numerical presentation of risk is always incomplete and often misleading. For this reason, the NRC (1) and EPA risk assessment guidelines (2) call for "characterizing" risk to include qualitative information, a related numerical risk estimate and a discussion of uncertainties, limitations, and assumptions.

Qualitative information on methodology, alternative interpretations, and working assumptions is an important component of risk characterization. For example, specifying that animal studies rather than human studies were used in an assessment tells others that the risk estimate is based on assumptions about human response to a particular chemical rather than human data. Information that human exposure estimates are based on the subjects's presence in the vicinity of a chemical accident rather than tissue measurements defines known and unknown aspects of the exposure component of the study.

Qualitative descriptions of this kind provide crucial information that augments understanding of numerical risk estimates. Uncertainties such as these are

expected in scientific studies and in any risk assessment based on these studies. Such uncertainties do not reduce the validity of the assessment. Rather, they are highlighted along with other important risk assessment conclusions to inform others fully on the results of the assessment.

2. Well-balanced risk characterization presents information for other risk assessors, EPA decision-makers, and the public regarding the strengths and limitations of the assessment.

The risk assessment process calls for identifying and highlighting significant risk conclusions and related uncertainties partly to assure full communication among risk assessors and partly to assure that decision-makers are fully informed. Issues are identified by acknowledging noteworthy qualitative and quantitative factors that make a difference in the overall assessment of hazard and risk, and hence in the ultimate regulatory decision.

The key word is "noteworthy": information that significantly influences the analysis is retained — that is, noted — in all future presentations of the risk assessment and in the related decision. Uncertainties and assumptions that strongly influence confidence in the risk estimate require special attention.

As discussed earlier, two major sources of uncertainty are variability in the factors upon which estimates are based and the existence of fundamental data gaps. This distinction is relevant for some aspects of the risk characterization. For example, the central tendency and high end individual exposure estimates are intended to capture the variability in exposure, lifestyles, and population. Key considerations underlying these risk estimates should be fully described. In contrast, scientific assumptions are used to bridge knowledge gaps such as the use of scaling or extrapolation factors and the use of a particular upper confidence limit around a dose-response estimate. Such assumptions need to be discussed separately, along with the implications of using alternative assumptions.

For users of the assessment and others who rely on the assessment, numerical estimates should never be separated from the descriptive information that is integral to risk characterization. All documents and presentations should include both; in short reports, this information is abbreviated but never omitted.

For decision-makers, a complete characterization (key descriptive elements along with numerical estimates) should be retained in all discussions and papers relating to an assessment used in decision-making. Fully visible information assures that important features of the assessment are immediately available at each level of decision-making for evaluating whether risks are acceptable or unacceptable. In short, differences in assumptions and uncertainties, coupled with non-scientific considerations called for in various environmental statutes, can clearly lead to different risk management decisions in cases with ostensibly identical quantitative risks; i.e, the "number" alone does not determine the decision.

Consideration of alternative approaches involves examining selected plausible

options for addressing a given uncertainty. The key words are "selected" and "plausible;" listing all options, regardless of their merits would be superfluous.

Generators of the assessment should outline the strengths and weaknesses of each alternative approach and as appropriate, estimates of central tendency and variability (e.g., mean, percentiles, range, variance.)

Describing the option chosen involves several statements.

1. A rationale for the choice.
2. Effects of option selected on the assessment.
3. Comparison with other plausible options.
4. Potential impacts of new research (on-going, potential near-term and/or long-term studies).

For users of the assessment, giving attention to uncertainties in all decisions and discussions involving the assessment, and preserving the statement of confidence in all presentations is important. For decision-makers, understanding the effect of the uncertainties on the overall assessment and explaining the influence of the uncertainties on the regulatory decision.

Section 3. Exposure Assessment And Risk Descriptors

The results of a risk assessment are usually communicated to the risk manager in the risk characterization portion of the assessment. This communication is often accomplished through risk descriptors which convey information and answer questions about risk, each descriptor providing different information and insights. Exposure assessment plays a key role in developing these risk descriptors, since each descriptor is based in part on the exposure distribution within the population of interest. The Risk Assessment Council (RAC) has been discussing the use of risk descriptors from time to time over the past two years.

The recent RAC efforts have laid the foundation for the discussion to follow. First, as a result of a discussion paper on the comparability of risk assessments across the Agency programs, the RAC discussed how the program presentations of risk led to ambiguity when risk assessments were compared across programs. Because different assessments presented different descriptors of risk without always making clear what was being described, the RAC discussed the advisability of using separate descriptors for population risk, individual risk, and identification of sensitive or highly exposed population segments. The RAC also discussed the need for consistency across programs and the advisability of requiring risk assessments to provide roughly comparable information to risk managers and the public through the use of a consistent set of risk descriptors.

The following guidance outlines the different descriptors in convenient order that should not be construed as a hierarchy of importance. These descriptors

should be used to describe risk in a variety of ways for a given assessment's purpose, the data available, and the information the risk manager needs. Use of a range of descriptors instead of a single descriptor enables Agency programs to present a picture of risk that corresponds to the range of different exposure conditions encountered for most environmental chemicals. This analysis, in turn, allows risk managers to identify populations at greater and lesser risk and to shape regulatory solutions accordingly.

EPA risk assessments will be expected to address or provide descriptions of (1) individual risk to include the central tendency and high end portions of the risk distribution, (2) important subgroups of the population such as highly exposed or highly susceptible groups or individuals, if known, and (3) population risk. Assessors may also use additional descriptors of risk as needed when these add to the clarity of the presentation. With the exception of assessments where particular descriptors clearly do not apply, some form of these three types of descriptors should be routinely developed and presented for EPA risk assessments. Furthermore, presenters of risk assessment information should be prepared to routinely answer questions by risk managers concerning these descriptors.

It is essential that presenters not only communicate the results of the assessment by addressing each of the descriptors where appropriate, but they also communicate their confidence that these results portray a reasonable picture of the actual or projected exposures. This task will usually be accomplished by highlighting the key assumptions and parameters that have the greatest impact on the results, the basis or rationale for choosing these assumptions/parameters, and the consequences of choosing other assumptions.

In order for the risk assessor to successfully develop and present the various risk descriptors, the exposure assessment must provide exposure and dose information in a form that can be combined with exposure-response or dose-response relationships to estimate risk. Although there will be differences among individuals within a population as to absorption, intake rates, susceptibility, and other variables such that a high exposure does not necessarily result in a high does or risk, a moderate or highly positive correlation among exposure, dose, and risk is assumed in the following discussion. Since the generation of all descriptors is not appropriate in all risk assessments and the type of descriptor translates fairly directly into the type of analysis that the exposure assessor must perform, the exposure assessor needs to be aware of the ultimate goals of the assessment. The following sections discuss what type of information is necessary.

1. Information about individual exposure and risk is important to communicating the results of a risk assessment.

Individual risk descriptors are intended to address questions dealing with

risks borne by individuals within a population. These question can take the form of:

- Who are the people at the highest risk?
- What risk levels are they subjected to?
- What are they doing, where do they live, etc., that might be putting them at this higher risk?
- What is the average risk for individuals in the population of interest?

The "high end" of the risk distribution is, conceptually, above the 90th percentile of the actual (either measured or estimated) distribution. This conceptual range is not meant to precisely define the limits of this descriptor, but should be used by the assessor as a target range for characterizing "high end risk." Bounding estimates and worst case scenarios[1] should not be termed high end risk estimates.

> The high end risk descriptor is a plausible estimate of the individual risk for those persons at the upper end of the risk distribution. The intent of this descriptor is to convey an estimate of risk in the upper range of the distribution, but to avoid estimates which are beyond the true distribution. Conceptually, high end risk means risks above about the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest risk.

This descriptor is intended to estimate the risks that are expected to occur in small but definable "high end" segments of the subject population. The individuals with these risks may be members of a special population segment or individuals in the general population who are highly exposed because of the inherent stochastic nature of the factors which give rise to exposure. Where no particular differences in sensitivity can be identified within the population, the high end risk will be related to the high end exposure or dose.

In those few cases where the complete data on the population distributions of exposure and doses are available, high end exposure or dose estimates can be represented by reporting exposures or doses at selected percentiles of the distributions,

[1] High end estimates focus on estimates of the exposure or dose in the actual populations. "Bounding estimates," on the other hand, purposely overestimate the exposure or dose in an actual population for the purpose of developing a statement that the risk is "not greater than. …" A "worst case scenario" refers to a combination of events and conditions such that, taken together, produce the highest conceivable risk. Although it is possible that such an exposure, dose, or sensitivity combination might occur in a given population of interest, the probability of an individual receiving this combination of events and conditions is usually small, and often so small that such a combination will not occur in a particular, actual population.

such as 90th, 95th, or 98th percentile. High end exposures or doses, as appropriate, can then be used to calculate high end risk estimates.

In the majority of cases where the complete distributions are not available, several methods help estimate a high end exposure or dose. If sufficient information about the variability in lifestyles and other factors are available to simulate the distribution through the use of appropriate modeling, e.g., Monte Carlo simulation, the estimate from the simulated distribution may be used. As in the method above, the risk manager should be told where in the high end range the estimate is being made by stating the percentile or the number of persons above this estimate. The assessor and risk manager should be aware, however, that unless a great deal is known about exposures and doses at the high end of the distribution, these estimates will involve considerable uncertainty which the exposure assessor will need to describe.

If only limited information on the distribution of the exposure or dose factors is available, the assessor should approach estimating the high end by identifying the most sensitive parameters and using maximum or near maximum values for one or a few of these variables, leaving others at their mean values[2]. In doing this, the exposure assessor needs to avoid combinations of parameter values that are inconsistent, e.g., low body weight used in combination with high intake rates, and must keep in mind the ultimate objective of being within the distribution of actual expected exposures and doses, and not beyond it.

If almost no data are available on the range for the various parameters, it will be difficult to estimate exposures or doses in the high end with much confidence, and to develop the high end risk estimate. One method that has been used in these cases is to start with a bounding estimate and "back off" the limits used until the combination of parameter values is, in the judgment of the assessor, clearly within the distribution of expected exposure, and still lies within the upper 10% of persons exposed. Obviously, this method results in a large uncertainty and requires explanation.

> The risk descriptor addressing central tendency may be either the arithmetic mean risk (Average Estimate) or the median risk (Median Estimate), either of which should be clearly labeled. Where both the arithmetic mean and the median are available but they differ substantially, it is helpful to present both.

The Average Estimate, used to approximate the arithmetic mean, can be derived by using average values for all the exposure factors. It does not necessarily

[2] Maximizing all variables will in virtually all cases result in an estimate that is above the actual values seen in the population. When the principal parameters of the dose equation (e.g., concentration, intake rate, duration) are broken out into subcomponents, it may be necessary to use maximum values for more than two of these subcomponent parameters, depending on a sensitivity analysis.

represent a particular individual on the distribution. The Average Estimate is not very meaningful when exposure across a population varies by several orders of magnitude or when the population has been truncated, e.g., at some point prescribed distance form a point source.

Because of the skewness of typical exposure profiles, the arithmetic mean is not necessarily a good indicator of the midpoint (median, 50^{th} percentile) of a distribution. A Median Estimate, e.g., geometric mean, is usually a valuable descriptor for this type of distribution, since half the population will be above and half below this value.

2. Information about population exposure leads to another important way to describe risk.

Population risk refers to an assessment of the extent of harm for the population as a whole. In theory, it can be calculated by summing the individual risks for all individuals within the subject population. This task, of course, requires a great deal more information than is normally, if ever, available.

Some questions addressed by descriptors of population risk include:

- How many cases of a particular health effect might be probabilistically estimated in this population for a specific time period?
- For noncarcinogens, what portion of the population are within a specified range of some benchmark level, e.g., exceedance of the RfD (a dose), the RfC (a concentration), or other health concern level?
- For carcinogens, how many persons are above a certain risk level such as 10^{-6} or a series of risk levels such as 10^{-5}, 10^{-4}, etc?

Answering these questions requires some knowledge of the exposure frequency distribution in the population. In particular, addressing the second and third questions may require graphing the risk distribution. These questions can lead to two different descriptors of population risk.

> The first descriptor is the probabilistic number of health effect cases estimated in the population of interest over a specified time period.

This descriptor can be obtained either by (a) summing the individual risks over all the individuals in the population when such information is available, or (b) through the use of a risk model such as carcinogenic models or procedures

which assume a linear non-threshold response to exposure. If risk varies linearly with exposure, knowing the mean risk and the population size can lead to an estimate of the extent of harm for the population as a whole, excluding sensitive subgroups for which a different dose-response curve needs to be used.

Obviously, the more information one has, the more certain the estimate of this risk description, but inherent uncertainties in risk assessment methodology place limitations on the accuracy of the estimate. With the current state of the science, explicit steps should be taken to assure that this descriptor is not confused with an actuarial prediction of cases in the population (which is a statistical prediction based on a great deal of empirical data).

Although estimating population risk by calculating a mean individual risk and multiplying by the population size is sometimes appropriate for carcinogen assessments using linear, non-threshold models[3] , this is not appropriate for non-carcinogenic effects or for other types of cancer models. For non-linear cancer models, an estimate of population risk must be calculated by summing individual risks. For non-cancer effects, we generally have not developed the risk assessment techniques to the point of knowing how to add risk probability, so a second descriptor, below, is more appropriate.

> Another descriptor of population risk is an estimate of the percentage of the population, or the number of persons, above a specified level of risk or within a specified range of some benchmark level, e.g., exceedance of the RfD or the RfC, LOAEL, or other specific level of interest.

This descriptor must be obtained through measuring or simulating the population distribution.

3. Information about the distribution of exposure and risk for different subgroups of the population are important components of a risk assessment.

A risk manager might also ask questions about the distribution of the risk burden among various segments of the subject population such as the following:

- How do exposure and risk impact various subgroups?
- What is the population risk of a particular subgroup?

Questions about the distribution of exposure and risk among such population segments require additional risk descriptors.

[3] Certain important cautions apply. These cautions are more explicitly spelled out in the Agency's Guidelines for Exposure Assessment, tentatively scheduled to be published in late 1991.

> Highly exposed subgroups can be identified, and where possible, characterized and the magnitude of risk quantified. This descriptor is useful when there is (or is expected to be) a subgroup experiencing significantly different exposures or doses from that of the larger population.

These subpopulations may be identified by age, sex, lifestyle, economic factors, or other demographic variables. For example toddlers who play in contaminated soil and certain high fish consumers represent subpopulations that may have greater exposures to certain agents.

> Highly susceptible subgroups can also be identified, and if possible, characterized and the magnitude of risk quantified. This descriptor is useful when the sensitivity or susceptibility to the effects for specific subgroups is (or is expected to be) significantly different from that of the larger population. In order to calculate risk for these subgroups, it will sometimes be necessary to use a different dose-response relationship.

For example, upon exposure to a chemical, pregnant women, elderly people, children, and people with certain illnesses may each be more sensitive than the population as a whole.

Generally, selection of the population segments is a matter of either a priori interest in the subgroup, in which case the risk assessor and risk manager can jointly agree on which subgroups to highlight, or a matter of discovery of a sensitive or highly exposed subgroup during the assessment process. In either case, once identified, the subgroup can be treated as a population in itself, and characterized the same way as the larger population using the descriptors for population and individual risk.

4. Situation-specific information adds perspective on possible future events or regulatory options.

These postulated questions are normally designed to answer "what if" questions, which are either directed at low probability but possibly high consequence events or are intended to examine candidate risk management options. Such questions might take the following form:

- What if a pesticide applicator applies this pesticide without using protective equipment?
- What if this site becomes residential in the future?
- What risk level will occur if we set the standard at 100 ppb?

The assumptions made in answering these postulated questions should not be confused with the assumptions made in developing a baseline estimate of exposure or with the adjustments in parameter values made in performing a sensitivity analysis. The answers to these postulated questions do not give information about how likely the combination of values might be in the actual population or about how many (if any) persons might be subjected to the calculated exposure or risk in the real world.

> A calculation of risk based on specific hypothetical or actual combinations of factors postulated within the exposure assessment can also be useful as a risk descriptor. It is often valuable to ask and answer specific questions of the "what if" nature to add perspective to the risk assessment.

The only information the answers to these questions convey is that if conditions A, B, and C are assumed, then the resulting exposure or risk will be X, Y, or Z, respectively. The values for X, Y, and Z are usually fairly straightforward to calculate and can be expresses as point estimates or ranges. Each assessment may have none, one, or several of these types of descriptors. The answers do not directly give information about how likely that combination of values might be in the actual population, so there are some limits to the applicability of these descriptors.

References

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2. U.S. EPA. Risk Assessment and Management: Framework for Decision Making. 1984.
3. U.S. EPA. Risk Assessment Guidelines. 51 Federal Register 33992-34054. September 24 , 1986.
4. Presentation of Risk Assessment of Carcinogens; Ad Hoc Study Group on Risk Assessment Presentation. American Industrial Health Council. 1989.

Appendix C

Calculation and Modeling of Exposure

This appendix describes some of the mathematical relationships and models used in exposure assessment.

Calculation Of Exposure

Assessing exposure to a pollutant requires information on the pollutant concentration at a specific location (microenvironment) and the duration of contact with a person or population. If the concentration of a pollutant to which a person is exposed can be measured or modeled and the time spent in contact with the pollutant is known, exposure is determined from concentration and time. When concentration varies with time, the total exposure from time t_1 to t_2 is given by

$$E = \int_{t_1}^{t_2} C(t)\,dt\,,$$

where E is the exposure of a person to a pollutant at concentration C; C(t) represents the functional relationship of concentration with time t for an interval t_1 through t_2. The average ("time-weighted average") exposure during this interval is $E/(t_2–t_1)$.

It is often assumed that the concentration is constant within a given microenvironment j for some finite interval, Δt_j. Thus, any particular exposure within a given microenvironment e_j is given by

$$e_j = \overline{C}_j \Delta t_j\,,$$

which means that a person stays within the microenvironment with average concentration

$\bar{C}_j$ for the interval Δt_j. A person's total exposure E to an airborne pollutant is the summation over all the microenvironments M in which the person is in contact with the pollutant:

$$E = \sum_{j=1}^{M} e_j = \sum_{j=1}^{M} \bar{C}_j \Delta t_j .$$

The latter equation includes the totality of all locations and activities that the person can occupy and engage in.

To obtain the total exposure of a population E_{pop} of N persons, it is necessary to sum the individual exposures E_i of all the persons in the population from $i = 1$ to N:

$$E_{pop} = \sum_{i=1}^{N} E_i = \sum_{i=1}^{N} \sum_{j=1}^{M} \bar{C}_j \Delta t_{ij} .$$

Generally, the amount of time spent in each microenvironment is averaged over the exposed population,

$$E_{pop} = N \sum_{j=1}^{M} \overline{C_j \Delta t_{ij}} ,$$

so that the average population exposure is given by

$$\overline{E_{pop}} = \sum_{j=1}^{M} \overline{C_j \Delta t_j} .$$

Thus, it is necessary to estimate the atmospheric concentration of the pollutant to which people are exposed to obtain C_j and their activity patterns to obtain Δt_j.

Modeling Of Exposure

It is often impossible or impractical to measure the exposures of individuals or populations directly, and instead mathematical models are used to estimate exposures. Microenvironmental concentrations are estimated with concentration models, which are based on the physics and chemistry of the environment. The time spend by an individual in a microenvironment with a pollutant is another important input to an exposure model. Population-exposure models combine data representing the time-activity patterns of an entire population with pollutant concentrations.

Gaussian-Plume Models

Gaussian-plume models are used by the Environmental Protection Agency (EPA) to estimate the concentration of a pollutant at locations some distance from an emission source. The models have this name because they represent the

plume of emissions from a stack as having a Gaussian, or normal, distribution, with a maximum at the center line, as shown in Figure C-1. The effect of boundaries (such as the ground or an atmospheric inversion cap), multiple emission sources, and deposition can alter the basic Gaussian distribution. Gaussian-plume models have been generalized to consider continuous and intermittent emissions, as well as emissions from points (e.g., concentrated emissions from a stack), areas (e.g., distributed emissions throughout a modeled region, such as home heating), and lines (e.g., roads). Gaussian-plume models have been further extended to complex topographic regions, such as valleys and bodies of water, and to industrial sources. They have also been designed for various temporal averaging periods. A number of Gaussian-plume models, with individual names, correspond to the various mathematical formulations used in the models. A few of the more commonly used Gaussian-plume models are the industrial-source complex long-term (ISCLT) and industrial-source complex short-term (ISCST) models, for long- and short-term averaging times, respectively; LONGZ (basic long-term model); Complex (for complex terrain); and Valley (for valleys). These are parts of the EPA UNAMAP modeling library (see Zannetti, 1990, for a brief description of each one and how to obtain the models).

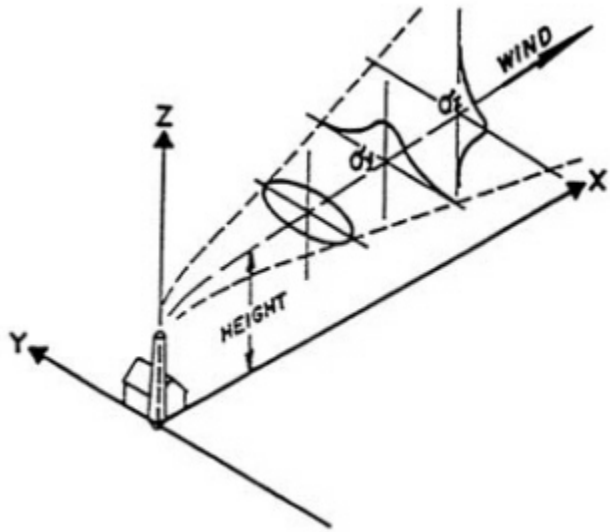

FIGURE C-1 Visualization of the dispersion of pollutants as described by a Gaussian-plume model.
Source: Russell, 1988. Reprinted with permission; copyright 1988, Health Effects Institute, Cambridge, Mass.

Gaussian-plume models are among the simplest atmospheric-dispersion models, but they can still involve a number of complexities. For example, many sources emit their effluent at higher than ambient temperatures, so their pollutants tend to rise. The rise is a complex process to describe, requiring the simultaneous consideration of heat and mass transfer, atmospheric turbulence, and source characteristics. Conversely, a pollutant may be emitted without sufficient buoyancy or momentum to be lifted above the wake of turbulent air downwind of a building or a topographic feature. The pollutants can then be caught in the wake and downwashed, increasing the potential exposure. Specific Gaussian-plume models, such as the ISCLT and ISCST models, have been developed for that possibility (EPA, 1987). The ISCLT and ISCST models are often suggested for use in exposure assessment of air pollutants from industrial sources. The Human-Exposure Model (described below), which is used by EPA, also uses the industrial-source complex models. Multiple sources are treated by superimposing the calculated contributions of individual sources. It is possible to include the first-order chemical decay of pollutant species within the Gaussian-plume framework, as well as deposition of both gases and particles.

Although Gaussian-plume models have been used for many years, their results are still subject to considerable error. In many cases, especially far from the source, they are biased to predict high concentrations. Applying Gaussian-plume models in complex terrain (such as hilly areas or areas with tall buildings) leads to even greater uncertainties and can result in significant overprediction and underprediction. Their rather simple formulation makes it difficult to handle complex terrain.

Human-Exposure Model

The HEM, one of the more commonly used models developed for EPA, incorporates a simple Gaussian-plume dispersion model with a fixed-location population model. Although EPA has developed several Gaussian-plume dispersion models for which validation studies have been conducted, the HEM was constructed with a model that incorporates an alternative approach to estimating the horizontal and vertical dispersion rates. The model was then compared with the standard UNIMAP models issued by the EPA Office of Air Quality, Planning, and Standards as part of the National Ambient Air Quality Standards (NAAQS) State Implementation Plan process, and it was found that they generally agreed to within a factor of 3. No comparison with field-measurement data was reported. In the most recent version of the program, the ISCLT model was incorporated as the default dispersion model, so that multiple emission points within the source area could be modeled, rather than aggregating all the emissions at a single point source within the source complex.

It is possible to substitute concentration data from other dispersion models into the HEM. For example, LONGZ was used to model the dispersion of

arsenic from the ASARCO smelter in Tacoma, Wash. LONGZ is a complexterrain model that was optimized to reproduce the sulfur dioxide dispersion from this plant. However, it is not clear that it was adequately modified to take particle deposition into account, and it was found to overpredict the airborne concentration of arsenic by factors of 5-8 for distances of up to 3 km from the plant and factors of 1.6-1.8 for larger distances. Assays of arsenic in urine also suggested that the model substantially overestimated arsenic exposure.

For distributed sources, such as perchloroethylene from dry cleaners, area sources were used with emission rates proportional to area population. The dispersion model was modified to incorporate the additional dispersion that comes from surface roughness and heat-island effects. The correction is included by making some of the parameters depend on the city geographic area.

In the HEM, the population is based on data from the Bureau of the Census (enumeration district/block groups, ED/BGs). An ED/BG is the area containing on average about 800 people and can range from part of a single city block to several hundred square kilometers. The population of each ED/BG is assumed to be at the center of the population's geographic distribution (centroid). The pollutant concentration at that location is interpolated from the results of the dispersion model. The interpolation is logarithmic in the radial direction and linear in the azimuthal direction. The product of the population and the concentration summed over the total area is then the total annual population exposure.

NAAQS Exposure Model

The NAAQS exposure model (NEM) was developed to estimate exposure to the criteria pollutants (e.g., carbon dioxide, CO). In 1979, EPA began to develop this model by assembling a database of human activity patterns that could be used to estimate exposures to outdoor pollutants (Roddin et al., 1979). The data were then combined with measured outdoor concentrations in the NEM to estimate exposures to CO (Biller et al., 1981; Johnson and Paul, 1983). The NEM has recently been modified to include indoor exposures by incorporation of the Indoor Air Quality Model (IAQM) (Hayes and Lundberg, 1985). The IAQM is based on the recursive (stepwise) solution of a one-compartment mass-balance model and incorporates three basic indoor microenvironments: home, office or school, and transportation vehicle. It has been used to estimate distributions of ozone exposures (Hayes and Lundberg, 1985) and to evaluate mitigation strategies for indoor exposures to selected pollutants for five scenarios, such as exposure to CO from a gas boiler in a school (Eisinger and Austin, 1987).

Simulation of Human Air Pollution Exposure (SHAPE) Model

SHAPE (Ott, 1981) is a computerized simulation model that generates synthetic exposure profiles for a hypothetical sample of human subjects; the exposure

profiles can be summarized into exposure measures—say, integrated exposures—to estimate the distribution for the exposure measure of interest. The bulk of the model estimates the exposure profile for pollutants attributable to local sources; the contribution of remote sources is assumed to be the same as that of a background site where there is no local source. The total exposure is therefore estimated as the exposure due to local sources plus the ambient concentration at the background site.

For each person in the hypothetical sample, the model generates a profile of activities and pollutant concentrations attributable to local sources over a given period, such as a 24-hour period. The activity profiles are generated by a modified Markov model. A later version of SHAPE can accept given profiles of activities, instead of using simulation to generate the activity profiles. At the beginning of the profile, an initial microenvironment is generated according to a probability distribution with the time spent in it, generated according to a microenvironment-specific probability distribution: each microenvironment has a specific probability distribution for its duration. At the end of the duration, a transition into another microenvironment is generated according to a transition probability distribution with another duration. The procedure is repeated until the end of the given period. For each time unit, such as a minute, spent in a given microenvironment, a pollutant concentration is generated according to a microenvironment-specific probability distribution, and each microenvironment has a specific probability distribution for its pollutant concentration. All random values are generated independently of each other.

Convolution Model

Duan (1981) originally developed the convolution model for the integrated exposure attributable to local sources and later (1987) expanded it for a broader context. In this model, distributions of exposure are calculated from the distributions of concentrations observed in each defined microenvironment and the distribution of time spent in those microenvironments. Thus, distributions of exposure are calculated for a population by assuming that values of concentration and time can be independently drawn from the exposure distributions and combined to yield a series of individual exposures. The exposures can then be summed over time to yield a time-integrated exposure for an individual in the population. Enough cases are drawn to provide a distribution of exposures for the entire population.

Variance-Component Model

The variance-component model assumes that short-term pollutant concentrations comprise two components, a time-varying component and a time-invariant component. If neither the time-varying component nor the time-invariant

component is negligible, SHAPE and the convolution method can no longer be used; it is necessary to use the variance-component model, which can incorporate both the time-variant and the time-invariant components. Depending on the needs of the analyst, the two components can be either summed or multiplied to estimate the modeled concentration value. Contaminant concentrations are usually more variable at higher values, so the multiplicative form may often be more realistic.

It is first necessary to determine the distributions of the two components. If random samples of locales belonging to the same microenvironment are available and if there are continuous monitoring data for at least a random sample of locales, it is possible to estimate the distributions of time-varying and time-invariant components of the concentration directly. If integrated personal monitoring data are available, the methods described by Duan (1987) can be applied. Once those distributions are available, exposure distributions are estimated with a computer simulation similar to that in SHAPE. However, instead of generating a contaminant concentration for each time unit independently, as in SHAPE, values of the time-invariant and time-varying components for each time unit are generated and then combined to determine 1-minute average concentrations. The remainder of the simulation is identical with SHAPE.

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Appendix D

Working Paper for Considering Draft Revisions to the U.S. EPA Guidelines for Cancer Risk Assessment

Notice

THIS DOCUMENT IS A PRELIMINARY DRAFT. Until formal announcement by the U.S. Environmental Protection Agency is made in the **Federal Register,** the policies set forth in the 1986 **Guidelines for Carcinogen Risk Assessment**, as they are now interpreted, remain in effect. This working paper does not represent the policy of the U.S. Environmental Protection Agency with respect to carcinogen risk assessment.

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Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C.

Disclaimer

This document is a draft working paper for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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Working Paper For Considering Draft Revisions To The U.S. Epa Guidelines For Cancer Risk Assessment

This working paper identifies cancer risk assessment issues that some Agency scientists have been discussing as a basis for possible proposed revisions to EPA's 1986 Guidelines for Carcinogen Risk Assessment. The working paper is being given to other scientists to obtain early comment on the many issues that remain undeveloped or are still under discussion. The working paper is not a proposal. It has not been reviewed or approved by any EPA official, and the proposal that is eventually approved is likely to be very different in many respects from this working paper. When proposed revisions are ready, EPA will publish them in the Federal Register for public comment.

Until formal announcement by the U.S. Environmental Protection Agency is made in the Federal Register, the policies set forth in the 1986 Guidelines for Carcinogen Risk Assessment, as they are now interpreted, remain in effect. This working paper does not represent the policy of the U.S. Environmental Protection Agency with respect to carcinogen risk assessment.

Preamble

The United States Environmental Protection Agency (EPA) 1986 guidelines on carcinogenic risk assessment (51 FR 33992, September 24, 1986)) stated that, "… [a]t present, mechanisms of the carcinogenesis process are largely unknown …". This is no longer true. The last several years have brought research results at an explosive pace to elucidate the molecular biology of cancer. This new knowledge is only beginning to be applied in generating data about environmental agents. Guideline revisions are intended to be flexible and open to the use of such new kinds of data even though the guidelines cannot fully anticipate the future forms that carcinogenicity testing and research may take. At the same time, the guidelines address assessment of the kinds of data that are the current basis of carcinogenicity assessment as a result of the past two decades of development of the science of risk assessment. Because methods and knowledge are expected to change more rapidly than guidelines can practicably be revised, most of the Agency's development of procedures for cancer risk assessment will henceforth be accomplished through publication of technical work performed under the aegis of the Agency's Risk Assessment Forum. The technical documents of the Forum are developed by a process that engages the general scientific community with EPA scientists. The documents are made available for public examination as well as for scientific peer review through the EPA Science Advisory Board and other groups. The Forum sponsored two workshops in which areas of potential revision to the guidelines were discussed by scientists from public and private groups. (USEPA, 1989a; USEPA, 1991a).

Major Changes from 1986 Guidelines

Revisions in this working paper differ in many respects from the Agency's 1986 guidelines. The reasons for change arise from new research results, particularly about the molecular biology of cancer, and from experience using the 1986 guidelines.

One area of change is increased emphasis on providing characterization discussions for each part of a risk assessment (hazard, dose-response, exposure, and risk assessments). These serve to summarize the assessments with emphasis on explaining the extent and weight of evidence, major points of interpretation and rationale, strengths and weaknesses of the evidence and analysis, and alternative conclusions that deserve serious consideration.

Two other areas of major change are in:

(1) the way the weight of evidence about an agent's[1] hazard potential is expressed; and

[1] The term "agent" is used throughout (unless otherwise noted) for a chemical substance, mixture, or physical or biological entity that is being assessed.

(2) approaches to dose-response assessment.

1. To express the weight of evidence for carcinogenic hazard potential, the 1986 guidelines provided tiered summary rankings for human studies and for animal bioassays. These summary rankings of evidence were integrated to place the overall evidence in alphanumerically designated classification groups A through E, Group A being associated with the greatest probability of carcinogenicity. Other experimental evidence played a modulating role for ranking. Considerations such as route of exposure (e.g., oral versus inhalation) and mechanism of action were not explicitly captured in a characterization.

These working revisions take a different approach. The idea of summary ranking of individual kinds of evidence is retained and expanded, but these are integrated differently and expressed in a narrative weight of evidence characterization statement. ***{Whether an alphanumerical rating will be a part of this statement is an unresolved issue still under discussion at EPA.}***

The narrative statement is preceded by summary rankings of human observational evidence and of all experimental evidence. The summary ranking for experimental evidence is composed of long-term animal bioassay evidence and all other experimental evidence on biological and chemical attributes relevant to carcinogenicity. This stepwise approach anticipates marshalling evidence and organizing conclusions as analysis proceeds, for convenience of consideration. It also gives explicit weight to certain kinds of experimental evidence that previously were considered in a "modulating" role.

The narrative statement provides a place to describe evidence by route of exposure and to describe the hazard assessment and dose-response implications of mechanism of action data in characterizing the overall weight of evidence about human carcinogenicity.

2. The approach to dose-response assessment is another area of major change. It calls for a stepwise analysis that follows the conclusions reached in the hazard assessment as to potential mechanism of action. Two steps divide the analysis into modeling in the range of observed data and analysis of dose-response below the range of observed data.

{The process for combining all the findings relevant to human carcinogenic potential is a matter of continuing discussion at EPA. This working paper presents one of a number of suggested approaches. The objective is to be integrative and holistic in judging while at the same time giving guidance to junior scientists in various disciplines about how to marshal and present findings.}

{How to use mechanistic information in dose-response assessment is incompletely

developed in these working paper. Specific issues are pointed out in later sections.}

Perspectives for Carcinogenicity Assessment

The following paragraphs summarize part of the current picture of the events in the process of carcinogenesis. Most of the research cited was conducted with experimental approaches not commonly used to study environmental agents. Nevertheless, as this picture is elaborated, more experimental approaches will become available for testing specific mechanisms of action of environmental agents. Even before this happens as a general forward step, information currently available for some agents can be interpreted in light of this picture to make informed inferences about the role the agent may play at the molecular level.

Normally, cell growth in tissues is controlled by a complex and incompletely understood process governing the occurrence and frequency of mitosis (cell division) and cellular differentiation. Adult tissues, even those composed of rapidly replicating cells, maintain a constant size and cell number (Nunez et al., 1991). This appears to involve a balance among three cell fates: (1) continued replication or loss of ability to replicate, followed by (2) differentiation to take on a specialized function or (3) programmed cell death (Raff, 1992; Maller, 1991; Naeve et al., 1991; Schneider et al., 1991; Harris, 1990). As a consequence of either the inactivation of processes that lead to differentiation or cell death, replicating cells may have a competitive growth advantage over other cells, and neoplastic growth clonal expansion can result (Sidransky et al., 1992; Nowell, 1976).

The path a cell takes is determined by a timed sequence of biochemical signals. Signal transduction pathways, or "circuits" in the cell, involve chemical signals that bind to receptors, generating further signals in a pathway whose target in many cases is control of transcription of a specific set of genes (Hunter, 1991; Cantley et al., 1991; Collum and Alt, 1990). A cell produces its own constituent receptors, signal transducers, and signals, and is subject to signals produced by other cells, either neighboring ones or distant ones, for instance, in endocrine tissues (Schuller, 1991). In addition to hormones produced by endocrine tissues, numerous soluble polypeptide growth factors have been identified that control normal growth and differentiation (Cross and Dexter, 1991; Wellstein et al., 1990). The cells responsive to a particular growth factor are those that express transmembrane receptors that specifically bind the growth factor.

One can postulate many ways to disrupt this kind of growth control circuit, including increasing or decreasing the number of signals, receptors, or transducers, or increasing or decreasing their individual efficiencies. In fact, human genetic diseases that make individuals cancer-prone involve mutations that appear to have some of these effects (Hsu et al., 1991; Srivastava, 1990; Kakizuka et al., 1991). Tumor cells found in individuals who do not have genetic disease

have also been shown to have mutations with these consequences (Salomon et al., 1990; Bottaro et al., 1991; Kaplan et al., 1991; Sidransky et al., 1991). For example, neoplastic cells of individuals with acute promyelocytic leukemia (APL) have a mutation that blocks cell differentiation in myeloblasts that normally give rise to certain white cells in blood. The mutation apparently alters a receptor that normally responds positively to a differentiation signal. Patients with APL involving this mutation have been successfully treated by oral administration of retinoic acid, which functions as a chemical signal that apparently overrides the effect of the mutation, and drives the neoplastic cells to stop replicating and differentiate. This "differentiation therapy" demonstrates the power conveyed by understanding the growth control signals of these cells (Kakizuka et al., 1991; de The et al., 1991).

Several kinds of gene mutations[2] have been found in human and animal cancers. Among these are mutations in genes termed tumor susceptibility genes. One kind, mutations that amplify positive signals to replicate or avert differentiation, are termed oncogenes (proto-oncogenes in their normal state). Another kind are mutations in genes involved in generating negative growth signals, termed tumor suppressor genes (Sager, 1989). Damage to these two kinds of genes has been found in cells of tumors in many animal and human tissues including the sites of the most frequent human cancers (Bishop, 1991; Malken et al., 1990; Srivastava et al., 1990; Hunter, 1991). The functions and deoxyribonucleic acid (DNA) base sequences of the genes are highly conserved across species in evolution (Auger et al., 1989a, b; Kaplan, 1991; Hollstein et al., 1991; Herschman, 1991; Strausfeld et al., 1991; Forsburg and Nurse, 1991). Some 100 oncogenes and several tumor suppressor genes have thus far been identified; specific functions are known for only a few.

The growth control circuit can also be altered without permanent genetic change by, for example, affecting the responsiveness of signal receptors, the concentration of signals, or the level of gene transcription (Holliday, 1991; Cross and Dexter, 1991; Lewin, 1991). These can come about through mimicry or inhibition of a signal or through physiological changes such as alteration of hormone levels that influence cell growth generally in some tissues.

Current reasoning holds that cell proliferation which results from changes at the levels of DNA sequence or DNA transcription, from changes at the level of growth control signal transduction, or from cell replication to compensate for toxic injury to tissue can begin a process of neoplastic change by increasing the number of cells that are susceptible to further events that may lead to uncontrolled growth. Such further events may include, for instance, errors in DNA replication that occur normally at a low background rate or effects of exposure to

[2] The term "mutations" includes the following permanent structural changes to DNA: single base-pair changes, deletions, insertions, transversions, translocations, amplifications, and duplications.

mutagenic agents. Effects on elements of the growth control circuit, both permanent and transient, probably occur continuously in virtually all animals due to endogenous causes. Exogenous agents (e.g., radiation, chemicals, viruses) also are known to influence this process in a variety of ways.

Endogenous events and exogenous causes such as chemical exposure appear to increase the probability of occurrence of cancer by increasing the probability of occurrence of effects on one or more parts of the growth control circuit. The specific effect of one exogenous chemical, aflatoxin B1, on a tumor suppressor gene has been postulated on the basis of molecular epidemiology. Mutations in the tumor suppressor gene p53 are commonly found in the more prevalent human cancers, e.g., colon carcinomas, lung cancer, brain and breast tumors (Levine et al., 1991; Malkin et al., 1990). Populations with high exposure to aflatoxin B1 have a high incidence of hepatocellular carcinoma showing a base change at a specific codon in the p53 gene (Hollstein et al., 1991). However, the patterns of base changes in this gene that are found in virus-associated hepatocellular carcinomas and at other sites of sporadic tumors showing p53 gene mutation are different from the pattern found in aflatoxin B1-exposed populations, supporting the postulate that the specific codon change is a marker of the effect of aflatoxin B1 (Hayward et al., 1991).

Research continues to reveal more and more details about the cell growth cycle and to shed light on the events in carcinogenesis at the molecular level. As molecular biology research progresses, it will become possible to better understand the potential mechanisms of action of environmental carcinogens. It has long been known that many agents that are carcinogenic are also mutagenic. Recognition of the role of oncogenes and mutations of tumor suppressor genes has provided specific ideas about the linkage of chemical mutagenesis to the cell growth cycle. Other agents that are not mutagenic, such as hormones and other chemicals that are stimulants to cell replication (mitogens), can be postulated to play their role by acting directly on signal pathways, for example as growth signals or by disrupting signal transduction (Raff, 1992; McCormick and Campisi, 1991; Schuller, 1991).

While much has been revealed about likely mechanisms of action at the molecular level, much remains to be understood about tumorigenesis. A cell that has been transformed, acquiring the potential to establish a line of cells that grow to a tumor, will probably realize that potential only rarely. The process of tumorigenesis in animals and humans is a multistep one (Bouk, 1990; Fearon and Vogelstein, 1990; Hunter, 1991; Kumar et al., 1990; Sukumar, 1989; Sukumar, 1990), and normal physiological processes appear to be heavily arrayed against uncontrolled growth of a transformed cell (Weinberg, 1989). Powerful inhibition by signals from contact with neighboring normal cells is one known barrier (Zhang et al., 1992). Another is the immune system (at least for viral infection). How a cell with tumorigenic potential acquires additional properties that are necessary to enable it to overcome these and other inhibitory processes is

unknown. For known human carcinogens studied thus far, there is an often decades-long latency between exposure to carcinogenic agents and development of tumors, which may suggest a process of evolution (Fidler and Radinsky, 1990; Tanaka et al., 1991; Thompson et al., 1989).

The events in experimental tumorigenesis have been described as involving three stages: initiation, promotion, and progression. The initiation stage has been used to describe a point at which a cell has acquired tumorigenic potential. Promotion is a stage of further changes, including cell proliferation, and progression is the final stage of further events in the evolution of malignancy (Pitot and Dragan, 1991). The entire process involves a combination of endogenous and exogenous causes and influences. The individual human's susceptibility is likely to be determined by a combination of genetic factors and medical history (Harris, 1989; Nebreda et al., 1991), lifestyle, diet, and exposure to chemical and physical agents in the environment.

A number of key questions about carcinogenesis have no generic answers —questions such as: How many events are required? Is there a necessary sequence of events? The answers to these questions may vary for different tissues and species even though the nature of the overall process appears to be the same. The fact that the nature of the process appears empirically to be the same across species is the basis for using assumptions that come from general knowledge about the process to fill gaps in empirical data on a particular chemical. Knowledge of the mechanisms that may be operating in a particular case must be inferred from the whole of the data and from principles on which there is some consensus in the scientific community.

Information from studies that support inferences about mechanism of action can have several applications in risk assessment. For human studies, analysis of DNA lesions in tumor cells taken from humans, together with information about the lesions that a putative tumorigenic agent causes in experimental systems, can provide support for or contradict a causal inference about the agent and the human effect (Vahakangas et al., 1992; Hollstein et al., 1991; Hayward et al., 1991).

An agent that is observed to cause mutations experimentally may be inferred to have potential for carcinogenic activity (U.S. EPA, 1991a). If such an agent is shown to be carcinogenic in animals the inference that its mechanism of action is through mutagenicity is strong. A carcinogenic agent that is not mutagenic in experimental systems, but is mitogenic or affects hormonal levels or causes toxic injury followed by compensatory growth may be inferred to have effects on growth signal transduction or to have secondary carcinogenic effects. The strength of these inferences depends in each case on the nature and extent of all the available data.

These differing mechanisms of action at the molecular level have different dose-response implications for the activity of agents. The carcinogenic activity of a direct-acting mutagen should be a function of the probability of its reaching

and reacting with DNA. The activity of an agent that interferes at the level of signal pathways with many potential receptor targets should be a function of multiple reactions. The activity of an agent that acts by causing toxicity followed by compensatory growth should be a function of the toxicity.

1. Introduction

1.1. Purpose And Scope Of The Guidelines

The new guidelines will revise and replace EPA Guidelines for Carcinogen Risk Assessment published in 51 FR 33992, September 24, 1896. Through guidelines, EPA provides its staff and decisionmakers with guidance and perspectives necessary to their performing and using risk assessments. Publication of EPA's guidelines also provides basic information about the Agency's approaches to risk assessment for those who participate in Agency proceedings, or in basic research or scientific commentary on the subjects the guidelines cover.

As the National Research Council pointed out in 1983 that there are many questions encountered in the risk assessment process that are unanswerable based on scientific knowledge (NRC, 1983). To bridge the uncertainty that exists in areas where there is no scientific consensus, inferences must be made to ensure that progress continues in the assessment process. While the application of scientific inferences is both necessary and useful, the bases for these inferences must be continually reviewed to assure that they remain consistent with predominating scientific thought.

The guidelines incorporate basic principles and science policies based on evaluation of the currently available information. Certain general assumptions are described that are to be used when data are incomplete. Standard, default assumptions are described in order to maintain consistency and comparability from one assessment to the next. However, these guidelines explain that such assumptions are to be displaced by facts or better reasoning when appropriate data are available. Short of displacement, an analysis of any promising alternatives is expected to be presented alongside default assumptions.

These guidelines serve two policy goals that must be balanced: first, to maintain consistency of procedures that will support regularity in Agency decisionmaking and, second, to be adaptable to advances in science. Each risk assessment must balance these goals. To assist in balancing these and other science policies, the Agency will rely on input from the general scientific community through the Agency's established scientific peer review processes. The Agency will continually adapt its practices to new developments in the science of environmental carcinogenesis, and restate or revise, where appropriate, the principles, procedures, and operating assumptions of the risk assessment process. Changes will be made through either revisions to these guidelines or, more

frequently, issuance of documents on scientific perspectives and procedures and science policies that are developed under the aegis of the EPA Risk Assessment Forum.

1.2. Types Of Data Used In Carcinogenicity Assessment

Under these guidelines all available direct and indirect evidence is considered to assess whether the weight of the combined evidence supports a conclusion about potential human carcinogenicity. Direct evidence for carcinogenicity in humans comes from epidemiological studies of cancer or, in a few instances, from case reports. Other data providing direct evidence can come from long-term animal cancer bioassays. Indirect evidence comes from a variety of information about toxicological and biochemical effects related to carcinogenicity.

The most direct evidence for identifying and characterizing an agent's human cancer hazard potential is from human epidemiologic studies in which cancer is attributed to exposure to a specific agent. These studies are rarely available because the identification and follow up of populations of sufficient size and sufficient exposure to detect underlying risk is rarely feasible. Moreover, exposure to many potential but unidentifiable causative factors is frequent, making statistical attribution of incidence of a cancer to a single agent difficult. Much of the human evidence comes from occupational studies in which workplace exposure to an agent has been high, and the increased incidence of a cancer attributed to the agent has been distinguishable from other potential causes. Studies that are statistically not powerful enough to discern as association between environmental exposure and tumor incidence or to distinguish among potential causative factors are unable to show that an agent is not carcinogenic. Such studies, if well conducted, may nevertheless be used to estimate a "ceiling" on an agent's carcinogenic potency.

Long-term animal cancer bioassays are more frequently available for more agents than are epidemiologic studies. Approximately 400 of these have been conducted by the National Cancer Institute and National Toxicology Program (NTP)(Huff et al., 1988; NTP, 1992) and many additional ones have been conducted by others. The correspondence between positive results in human studies and long-term animal cancer bioassays is high (Tomatis et al., 1989; Rall, 1991) in the limited number of cases in which comparison is possible. In the absence of epidemiologic information, tumor induction in animal assays remains the best single piece of direct evidence on which to evaluate potential human carcinogenic hazard (OSTP, 1985). Results of animal studies have to be carefully analyzed along with other relevant data (such as metabolism and pharmacokinetic data used to compare animals and humans) to evaluate biological significance, causation, and reproducibility of results, and to determine the reasonable inferences about human hazard they support (Allen et al., 1988; Ames and Gold, 1990).

Data on physicochemical characteristics and biological effects of an agent

that make it more or less likely to affect processes involved in producing neoplasia provide important evidence supporting influences about carcinogenic potential. These include, for example, the ability to alter genetic information, influences on cell growth, differentiation, and death, and structural and functional analogies to other compounds that are carcinogenic.

1.3. Organization Of The Guidelines

These guidelines follow and should be read with two other publications that provide basic information and general principles. These are: Office of Science and Technology Policy (OSTP, 1985) *Chemical Carcinogens: A Review of the Science and its Associated Principles* (50 FR 10371), and National Research Council (NRC, 1983), *Risk Assessment in the Federal Government: Managing the Process* (Washington, DC, National Academy Press). The 1983 NRC document provided the 1986 guidelines with a thematic organization of risk assessment into hazard identification, dose-response assessment, exposure assessment, and risk characterization. This thematic organization has been slightly revised in these guidelines to focus attention on the importance of characterization in each part of the assessment. Nonetheless, the four questions addressed in these four areas remain the same; they are: Can the agent present a carcinogenic hazard to humans? At what levels of exposure? What are the conditions of human exposure? What is the overall character of the risk, and how well do data support conclusions about the nature and extent of the risk?

1.4. Application Of The Guidelines

The guidelines are to be used within the policy framework already provided by applicable EPA statutes and do not alter such policies. The Guidelines provide general directions for analyzing and organizing available data. They do not imply that one kind of data or another is prerequisite for regulatory action to control, prohibit, or allow the use of a carcinogen.

Regulatory decision making involves two components: risk assessment and risk management. Risk assessment defines the adverse health consequences of exposure to toxic agents. The risk assessments will be carried out independently from considerations of the consequences of regulatory action. Risk management combines the risk assessment with directives of regulatory legislation, together with socioeconomic, technical, political, and other considerations, to reach a decision as to whether or how much to control future exposure to the suspected toxic agents.

2. Hazard Assessment

2.1. Introduction

Hazard assessment covers a wide variety of data relevant to the question, can an agent pose a human carcinogenic hazard? Available data may include: long term animal cancer bioassays and human studies, physical-chemical properties of the agent and its structural relationship to other carcinogens, studies of cellular and molecular interactions and mechanisms of action, and results from toxicological tests and experiments on the bioavailability and transformation of an agent in experimental animals and humans. Hazard assessment results are summarized in a hazard characterization that conveys the nature and impact of available data and appropriate scientific inferences about human carcinogenic hazard.

Experience shows that the nature and extent of information available on each agent is different and can vary from a wealth of epidemiologic data to only physical-chemical properties. Frequently, results from a long-term animal carcinogenesis bioassay are the only direct evidence available for the evaluation. These guidelines follow the assumption that chemicals with evidence to demonstrate carcinogenicity in animal studies are likely to present a carcinogenic hazard to humans under some conditions of exposure (OSTP, 1985). At the same time, there may be mechanistic, physiological, biochemical, or route-of-entry differences which alter the toxicological consequences in humans from those observed in the particular animals tested. When the results of animal testing are extrapolated to humans, effects observed at high continuous exposures are often projected to low or intermittent exposures and results from one route of exposure are often extrapolated to other routes of exposure. The risk analysis must examine each assumption and extrapolation for mechanistic and biological plausibility. The elements of hazard assessment described below are the foundation for these examinations.

The characterization of an agent's carcinogenic human hazard potential depends on the weight of all the relevant evidence. Studies are evaluated according to accepted criteria for study quality, sensitivity, and specificity. These have been described in several publications (Interagency Regulatory Liaison Group, 1979; OSTP, 1985; Peto et al., 1980; Mantel, 1980; Mantel and Haenszel, 1959; Interdisciplinary Panel on Carcinogenicity, 1984; National Center for Toxicological Research, 1981; National Toxicology Program, 1984; U.S. EPA, 1983a, b, c; Haseman, 1984). The hazard characterization describes how likely the agent is to be carcinogenic to humans, including the judgment whether or not the hazard is considered to be contingent on certain conditions of exposure (e.g., oral versus dermal exposure). The characterization summarizes the basis of, and confidence in, inferences drawn from data and the rationale for conclusions about

weight-of-evidence; these are accompanied by judgments on issues and uncertainties that cannot be resolved with available information.

The characterization of potential hazard is qualitative. It does not address the magnitude or extent of effects under actual exposure conditions. However, observations and conclusions from the hazard characterization that are relevant to quantitative dose-response analysis are carried forward to the section on quantitative dose-response analysis, and those that are relevant to actual exposure conditions are discussed in the risk characterization.

2.2. Integrating Data For Hazard Assessment

The assessment of potential carcinogenic hazard to humans is a process in which many kinds of data are integrated to examine the inferences and conclusions they support. The process is conducted as an interdisciplinary effort.

While the discussion that follows explores data analyses along separate disciplinary lines and provides for making intermediate summaries of human observational data and experimental data, it must be recognized that this is done simply for convenience of organization and marshalling of thought, and the individual analyses are interdependent not separate. Each kind of analysis, from evaluation of human studies to structure-activity relationship analysis, looks to the others for interpretive alliance and perspective. Confidence in conclusions is built upon the overall coherence of inferences from different kinds of data as well as confidence in individual data sets.

For example, in examining the issue of causation as part of human studies analyses, one uses knowledge of the biological activity of the agent in animal systems and of pertinent features of its structure, metabolism and other properties to address issues of biological plausibility of a causal hypothesis. Likewise, where there are no epidemiologic studies and one is examining relevance of animal responses to human hazard potential, one uses human data to address comparative biology of animals and humans with respect to, for instance, metabolism, pharmacokinetics, physiology, and disease history.

2.3. Analysis Of Human Data

2.3.1. Epidemiologic Studies

Epidemiology is the study of the distribution of a disease in a human population and the determinants that may influence disease occurrences. Epidemiologic studies provide direct information about the response of humans who have been exposed to suspect carcinogens and avoids the need for interspecies extrapolation of animal toxicological data.

2.3.1.1. Exposure Focus

An identification of hazard in a human population depends critically on the exposure assessment, which consists of two components: (a) the qualitative determination of the presence of an agent in the environment and (b) the quantitative assessment. An exposure assessment which includes an attribution of quantified exposure to an individual is considered more precise and will carry more weight in an evaluation of human hazard. In many epidemiologic studies, the populations are selected and studied retrospectively, and the time between exposure and observation of effects is very long because of the latency of cancer. The past exposure is a critical determinant. In an environmental situation, quantitative exposure assessment is usually difficult to achieve due to lack of measures of past exposure. This is one reason why occupational studies where exposure is based on job classification are often used for identifying environmental hazard. Past occupational exposures are usually considered to be at higher levels than those encountered environmentally; therefore, the question whether any identified hazard is pertinent at lower exposure levels needs to be addressed.

Exposure assessment becomes more complicated when the exposure is to a complex mixture of incompletely identified chemicals. In addition, human exposures to agents can occur by more than one route as compared to the controlled exposure regimens used in the animal carcinogenicity studies (e.g., occupational exposure to solvents can occur through inhalation and dermal absorption). The characterization of the patterns of exposure to identify exposure-effect relationships is another consideration. Important exposure measurements in epidemiologic studies include cumulative exposure (sometimes time-weighted), duration of exposure, peak exposure, exposure frequency or intensity, and "dose" rate. Some insight on which measurement of exposure will be the best predictor of a cancer can come from an understanding of the disease process itself.

In epidemiological studies, "biological markers," usually the reaction products of an agent or its metabolite with DNA or a protein or other markers of exposure such as excretion of metabolites in urine have been increasingly considered as reliable measures of exposure. More rarely a marker of *effect* specific to an agent may be found (Vahakangas et al., 1992). Information on the relationship between exposure or effect and markers is often derived from metabolism and kinetic studies in animals. Validation of the relationship with comparative human data is needed to support confidence in use of such markers.

{The generic issue of use biomarker of exposure and effect is still under consideration.}

2.3.1.2. Types of Epidemiology Studies

Various types of epidemiologic studies or reports can provide useful information for identifying hazards. An important consideration is the validity and representativeness of the studied population with respect to the larger population of interest. Study designs include cohort, case-control, proportionate ratio, clinical trials, and correlational studies. In addition, cluster investigations and case reports, while not constituting studies, may yield useful information under certain situations (e.g., reports associated with exposure to vinyl chloride and diethylstilbestrol). The above designs have well-defined strengths and limitations (Breslow et al., 1980; 1987; Kelsey et al., 1986; Lilienfeld and Lilienfeld, 1979; Mausner and Kramer., 1985; Rothman, 1986).

2.3.2. Elements of Critical Analysis

Aspects of the available human data, which are described in this section, are evaluated to determine whether there is a causal relationship between exposure to the agent and an increase in cancer incidence. Certain elements of analysis are brought to bear on the criteria for causality, which are listed and discussed in Section 2.3.2.5. In general, these elements address the study design and conduct; the ability to sort out the potential role of the agent in question as opposed to other risk factors; assessment of exposure of the study and referent populations to the agent and to other risk factors; and, given all of the above, the statistical power of the study or studies.

2.3.2.1. Exposure

Exposure is the foundation upon which any exposure-effect relationship is evaluated. Often, the exposure is not to a single agent, but to a combination of agents (e.g., exposure to chloromethylmethyl ether and its ever-present contaminant bischloromethyl ether). When exposures occur simultaneously, it is generally assumed that each chemical exposure contributes to the exposure- or exposures-effect relationship.

Exposure can be defined in hierarchical levels. Greater weight will be given to studies where exposures are more precisely defined and can be quantified. The broadest definition of exposure is that inferred for a group of individuals living in a geographic area. At this level, it is not known whether all individuals are exposed to the agent, and if exposed, the patterns and lengths of exposure. The result is a mixture of individuals with higher exposure and those with little or no exposure. This leads to exposure misclassification, which, if random, may result in a study's reduced ability to detect underlying elevations in risk. For the same reasons, exposure as defined by assignment to a broad occupational category

in the absence of qualitative or quantitative data yields less useful information on an individual's exposure.

A more recent application in epidemiologic studies is the use of job-exposure matrices to infer semi-quantitative and quantitative levels of exposure to specific agents (Stewart and Herrick, 1991). The job-exposure matrix has been applied to occupational scenarios where at least some current and historical monitoring data exist. In examining exposure levels inferred from a job-exposure matrix, the basis of the monitoring data must be considered—whether data are from routine monitoring or reflect accidental (i.e., higher than average) releases.

Biological markers are indicators of processing within a biological system. Using such a marker as a measure of exposure is potentially the most reliable level of data since the quantity measured is thought to more precisely characterize a biologically available dose, rather than exposure that is the amount of material presented to the individual and is usually inferred from a measurement of atmospheric concentrations (NAS, 1989). Validated markers are the most desirable, i.e., markers which are highly specific to the exposure and those which are highly predictive of disease (Blancato, OHR Biomarker Strategy, cite published paper; Hulka and Margolin, 1992) (e.g., urinary arsenic (Entertine et al., 1987), and alkylated hemoglobin (hemoglobin adducts) from exposure to ethylene oxide (Callemen et al., 1986; van Sittert et al., 1985).

2.3.2.2. Population Selection Criteria

The study population and the comparison or referent population are identified and examined to decide whether or not comparisons between populations are appropriate and to determine the extent of any bias resulting from their selection. The ideal referent population would be similar to the study population in all respects except exposure to the agent in question. Potential biases (e.g., healthy worker effect, recall bias, selection bias, and diagnostic bias) and the representativeness of the studied population for a much larger population are addressed.

Generally, the referent population in cohort studies consists of mortality or incidence rates of a larger population (e.g., the U.S. population). The healthy worker bias is specific to occupational cohort studies, and it asserts that an employed population is healthier than the general population (McMichael, 1976). The influence of the healthy worker effect is toward a more favorable mortality in the exposed population; this influence is thought to decrease with increasing age and to have less influence on site-specific cancer rates. The influence of the healthy worker effect is thought to be minimized by the use of an internal comparison group (e.g., incidence or mortality rates of employees who are from the same company, but not among the employees in the study population).

In case-control designs, the potential for differences in recalling past events (recall bias) between the case and control series needs to be evaluated. The

characteristics of the control series also need to be discussed. Hospital controls have associated limitations with respect to possible associations with the exposure of interest. Randomly-selected population or community controls are thought to be more like cases in the case series; however, response rates are often lower.

2.3.2.3. Confounding Factors

A confounding variable is a risk factor for the disease under study that is distributed unequally among the exposed and unexposed populations. Adjustment for possibly confounding factors can occur either in the design of the study (e.g., matching on critical factors) or in the statistical analysis of the results. If adjustment within the study data is not possible due to the presentation of the data or because needed information was not collected during the study, indirect comparisons may be made (e.g., in the absence of direct smoking data from the study population, an examination of the possible contribution of cigarette smoking to increased lung cancer risk and to the exposure in question may include information from other sources such as the American Cancer Society's longitudinal studies (Hammond, 1966; Garfinkel and Silverburg, 1991).

In a collection of heterogenous studies possible confounding factors are usually randomly distributed across studies. If consistent increases in cancer risk are observed across the collection of studies, greater weight is given to the agent under investigation as the etiologic factor even though the individual studies may not have completely adjusted for confounding factor.

2.3.2.4. Sensitivity

Epidemiologic studies which consist of a large number of individuals with sufficient exposure to a putative cancer-causing agent and adequate length of time for cancer development or detection are considered to have a greater ability to detect cancer risk. Studies for review, however, do not always fulfill these criteria. In addition, the ability to detect increases in relative risk associated with environmental exposure is very difficult due to heterogeneous exposure regarding both pattern and levels and which potentially bias risk toward the null hypothesis of no effect.

If the underlying risk is actually increased, examination of persons considered at higher risk increases the detection ability of a study. Such examination may include an evaluation of risk among individuals with higher or peak exposure, with greater duration of exposure, or with the longest time since first exposure (to allow for latency of effect), and those of older age, and those with long latencies.

A study in which no increases in risk were observed may be useful for inferring an upper limit on possible human risk. Statistical reanalysis is another

approach for examining the sensitivity of results from an individual study (e.g., the dose-response relationship reported in one formaldehyde-exposed cohort (Blair et al., 1986) has been examined by several investigators (Blair et al., 1987; Sterling and Weinkam, 1987; Collins et al., 1988; Marsh, 1992). These further analyses are a reaggregation of exposure groups or an examination of the influence of a subgroup on the disease incidence of the much larger group.

Statistical methods for examining several studies together are frequently applied to the collection of data. These methods, commonly referred to as meta-analysis, are used to contrast and combine results of different studies with the goal of increasing sensitivity. In meta-analysis, study results are evaluated as whether they differ randomly from the null hypothesis of no effect (Mann, 1990); meta-analysis presumes that observed results are not biased. If an underlying effect is not present, the observed results should appear randomly distributed and cancel each other when studies are combined (Mann, 1990). Several important issues are pertinent to meta-analysis. These are controlling for bias and confounding prior to combining studies, criteria for study inclusion, assignment of weights to individual studies, and possible publication and aggregation bias. Greenland, 1987 discusses may of these issues in addition to identifying methodologic approaches.

{Participants at the December 4, 1992, Society for Risk Analysis on cancer risk assessment issues were asked to look at meta-analysis.}

2.3.2.5. Criteria for Causality

A causal interpretation is enhanced for studies to the extent that they meet the criteria described below. None of the criteria, with the exception of a temporal relationship, should be considered as either necessary or sufficient in itself to establish causality. These criteria are modelled after those developed by Hill in the examination of cigarette smoking and lung cancer (Rothman, 1986).

a. *Temporal relationship*: This is the single absolute requirement, which itself does not prove causality, but which must be present if causality is to be considered. The disease occurs within a biologically reasonable time frame after the initial exposure. The initial period of exposure to the agent is the accepted starting point in most epidemiologic studies.
b. *Consistency*: Associations are observed in several independent studies of a similar exposure in different populations. This criterion also applies if the association occurs consistently for different subgroups in the same study.
c. *Magnitude of the association*: A causal relationship is more credible when the risk estimate is large and precise (narrow confidence intervals).

d. *Biological gradient*: The risk ratio is correlated positively with increasing exposure or dose. A strong dose-response relationship across several categories of exposure, latency, and duration is supportive although not conclusive for causality given that confounding is unlikely to be correlated with exposure. The absence of a dose-response relationship, however, should not be construed by itself as evidence of a lack of a causal relationship.

e. *Specificity of the association*: The likelihood of a causal interpretation is increased if a single exposure produces a unique effect (one or more cancers also found in other studies) or if a given effect has a unique exposure.

f. *Biological plausibility*: The association makes sense in terms of biological knowledge. Information from animal toxicology, pharmacokinetics, structure-activity relationship analysis and short-term studies of the agent's influence on events in the carcinogenic process are considered.

g. *Coherence*: The cause-and-effect interpretation is in logical agreement with what is known about the natural history and biology of the disease, i.e., the entire body of knowledge about the agent.

2.4 Summary Of Human Evidence

{The process in combining all findings relevant to human carcinogenic potential is an issue for further development. The need for this summarization step for human evidence and the one in Section 2.5 for experimental evidence are open questions at EPA.}

Each epidemiological study is critically evaluated for its relevance with respect to the exposure-effect relationship, exposure assessment such as intensity, duration, time since first exposure, and methodological issues such as study design, selection and characterization of comparison group, sample size, handling of latency, confounders, and bias.

Following critical evaluation, the totality of the weight-of-evidence for human carcinogenicity is assessed and summarized according to one of the following four categories, which are meant to represent a judgment regarding the weight of all of the human evidence even if only one study exists on the subject. Rarely, the judgment can be based on a series of case reports. More likely, the evaluation will involve several studies. Inferences from summary analyses such as meta-analysis can provide support for placement into these categories. In addition, evidence that the agent in question is metabolized to a compound, for which independent human evidence exists, is supportive of the categorization.

The weight a particular study or analysis is given in the evaluation depends on its design, conduct, and avoidance of bias (selection, confounding, and measurement)

(OSTP, 1984). Results, both positive and null, are considered in light of the study's rigor. The weight of evidence is based on the plausibility of the association and the conclusiveness of observed findings. Greater plausibility and conclusiveness can be ascribed to an exposure-effect relationship when it can be explained in terms of adherence to the criteria for causality, including coherence with other evidence such as animal toxicology. The plausibility of exposure-effect relationship also can be bolstered or mitigated by evidence of structure-activity relationship analysis with well characterized agents, studies of mechanism of action, understanding of metabolic pathways, and other indirect evidence relevant to human effects. A mixture (e.g., cigarette smoke, coke oven emissions) may be categorized as an agent when causation is ascribed to the mixture, but not to necessarily to its individual components.

2.4.1. Category 1

Plausible evidence exists, and from this evidence a conclusive causal association can be judged. Cause and effect relationships are supported with results from well-designed and conducted studies in which random or nonrandom error can be reasonably excluded.

2.4.2. Category 2

Evidence exists to suggest that causal association is plausible; however, such evidence is not conclusive due to a number of reasons which may include lack of consistency, wide confidence intervals which may or may not include a risk, or absence of an observed dose-response relationship. The effect of random or nonrandom error in individual studies which could influence the risk ratio away from the null is considered minimal. This category covers a broad range of possible weights of evidence. At the top of the category are highly suggestive, but short of convincing data. At the bottom of the category are suggestive but weak data. A statement of the relative position of data in this continuum accompanies the description of the data as Category 2.

2.4.3. Category 3

The body of evidence is inconclusive. The assertion of a causal association is not plausible from the available data in which studies of equal quality have contradictory results in which random or nonrandom error is a more likely explanation for observations of increased risk. This category also applies when no epidemiologic data are available.

2.4.4. Category 4

The available studies are designed with defined ability to detect increases in risk, and resultant risk ratios are precise with tight confidence intervals. Evidence derived from the studies consistently show no positive association between the suspect agent and cancer. The evidence is described as showing no cause and effect relationship at the exposure levels studied. It is not considered to show that the agent is non-carcinogenic under all circumstance unless the evidence is so complete that potential for human carcinogenicity can be eliminated.

2.5. Analysis Of Long-Term Animal Studies

Long-term animal studies are evaluated to decide whether biologically significant responses have occurred and whether responses are statistically significantly increased in treated versus control animals. The unit of comparison is an experiment of one sex, in one species.

2.5.1. Significance of Response

Evidence for carcinogenicity is based on the observation of biologically and statistically significant tumor responses in specific organs or tissues. Criteria for categorizing the strength of evidence of animal carcinogenicity in bioassays have been established by the National Toxicology Program (NTP, 1987). Animal study results are evaluated for adequacy of design and conduct (40 CFR Part 798). The results are described and biological significance of observed toxicity is evaluated (non-neoplastic endpoints included).

{For EPA's purposes, the criteria for evaluating animal cancer bioassays are still under review, and could be somewhat different from those of NTP. Nevertheless, much of the animal cancer data available to EPA carries the NTP designations of "clear, some, equivocal, or none".}

Interpretation of animal studies is aided by the review of target organ toxicity and other non-neoplastic effects (e.g., changes in the immune and endocrine systems) that may be noted in prechronic or other toxicological studies. Time and dose-related changes in the incidence of preneoplastic and neoplastic lesions may also be helpful in interpreting responses in long-term animal studies.

It is recognized that chemicals that induce benign tumors also frequently induce malignant tumors, and that certain benign tumors may progress to malignant tumors. Benign and malignant tumor incidence are combined for analysis of carcinogenic hazard when scientifically defensible (OSTP, 1985; Principle 8).

The Agency follows the National Toxicology Program framework for combining benign and malignant tumor incidence of a particular site (McConnell, 1986).

Elevated tumor incidences in adequate experiments are analyzed for biological and statistical significance. Generally, a statistical test that shows a positive trend in dose-response at a level of significance of five percent (i.e., the likelihood of false positive results is less than five percent) supports a conclusion that the experiment is positive. If false positive outcomes are a serious concern, the use of a formal multiple comparison adjustment procedure should be considered. No rigid decision rule should be used as substitute for scientific judgment. Other statistical tests may be applied if the trend test is not statistically significant or, for some reason, not applicable for a given experiment. The significance level should be adjusted if multiple comparisons of the same data are made, in order to avoid raising the overall likelihood of false positives (Haseman, 1983, 1990; U.S. FDA, 1987).

Data from all long-term animal studies, positive and negative, are to be considered in the evaluation of carcinogenicity. Different results according to species, sex, or strain, or by route of administration, duration of study or site of effect are not unexpected. The issues are how different results affect the weight of evidence and whether the differences suggest the operation of any particular mechanisms of action or tissue sensitivity that may assist in judging human relevance.

2.5.2. Historical Control Data

{NOTE TO THE READER: The issues of how to consider historical control data and high background tumors are knotty ones. For high background tumors there are varying views, some question relevance, but usually there are insufficient data about the mechanism of action to question its relevance. Others point to the fact that both humans and animals have tissues with high background rates.}

Historical control data often add valuable perspective in the evaluation of carcinogenic responses (Haseman et al., 1984). For the evaluation of rare tumors, even small increases in tumor response over that of the concurrent controls may be significant compared to historical data. Historical data can also identify sites with high spontaneous background in the test strain. Nevertheless, historical control data have limitations as compared to concurrent control data. One limitation is the potential for genetic drift in laboratory strains over time that makes historical data less useful beyond a few years. Other limitations are the differences in pathological examinations at different times and in different laboratories; these are due to changes over time in criteria for evaluating lesions and to variations in preparation techniques and reading of tissue samples between laboratories. Other differences may include biological and health differences in

animal strains from different suppliers. Concurrent controls are, for these reasons, more valuable comparison for judging whether observed effects in dosed animals are treatment related.

Comparison of an observed response that appears to be treatment related with historical control data may call the response into question if the observed response is well within the range of historical control data. Whenever historical control data are compared with the current data the reasons should be given for judging the historical control data to be adequately representative of the current expected response background.

2.5.3. High Background Tumor Incidence

Tumor data at sites with high spontaneous background requires special consideration (OSTP, 1985; Principle 9). Questions raised about high background tumors in animals (and humans) are whether they are due to particular genetic predispositions or ongoing proliferative processes that are species-specific prerequisites to a neoplastic response or, on the other hand, represent sensitivities due to biological processes that are alike among species. Answering these questions requires a body of research data beyond the data obtained in standard animal studies. Unless there are research data to establish that such tumor data at a site occur because of a mechanism-of-action that is unique to the species, strain, and sex with the high background, the tumor data are considered, as are other tumor data, in the overall weight of evidence. These data may receive relatively less weight than other tumor data.

2.5.4. Dose Issues

Long-term animal studies at or near the maximum tolerated dose level (MTD) are used to ensure an adequate power for the detection of carcinogenic activity of an agent (NTP, 1984; IARC, 1982). The MTD is a dose which is estimated to produce some minimal toxic effects in a long term study (e.g., a small reduction in body weight), but should not shorten an animal's life span or unduly compromise normal well-being except for chemically induced carcinogenicity (International Life Sciences Institute, 1984; Haseman, 1985). Assays in which the MTD may have been exceeded or may not have been reached require special scrutiny.

Exceedance of the MTD in a study may result in tumorigenesis that is secondary to tissue damage or physiological damage and is more a function of this damage than of the carcinogenic influence of the particular agent tested. Inferences drawn from the study must consider observed non-neoplastic toxicity and the tissues affected, as well as the existence of carcinogenic effects in tissues, or at doses, not affected by the exceedance. Study results at doses that exceed the

MTD can be rejected if toxic damage is so severe as to compromise interpretation.

Null results in long-term animal studies at exposure levels above the MTD may not be acceptable if animal survival is so impaired that the sensitivity of the study is significantly reduced below that of a conventional chronic animal study at the MTD. The import of non-positive studies at exposure levels below the MTD may be compromised by lack of power to detect effects.

2.5.5. Human Relevance

Relevance of tumor responses to human hazard is a judgment that is integral to analysis of bioassay results. The assumption is made under these guidelines that observation of tumors at any animal tissue site supports an inference that humans may respond at some site. This assumption is reexamined as data on the issue become available for specific responses. The Agency will undertake analyses of relevance issues as needed in reports to be published from time to time (e.g., USEPA, 1991b).

If information on the mechanism of tumorigenesis supports the conclusion that a response seen in an animal study is unique to that species or strain, the response is considered to provide no evidence for human hazard potential (U.S. EPA, 1991a). Agency decisions of this kind about particular animal responses are made and published under the aegis of the EPA Risk Assessment Forum. Such mechanistic uniqueness is be differentiated from quantitative differences in dose-response which are not, *per se*, issues of relevance.

2.6. Analysis Of Evidence Relevant To Carcinogenicity

Certain structural, chemical, and biological attributes of an agent provide key information about its potential to cause or influence carcinogenic events. These attributes and comparative studies between species provide information to support carcinogenic hazard identification and compare potential activity across species. The following sections provide guidance for inclusion of analyses of these kinds of evidence in hazard identification.

2.6.1. Physical-Chemical Properties

Physical-chemical properties that can affect the agent's absorption, tissue distribution (bioavailability), biotransformation, or chemical degradation in the body are analyzed as part of the overall weight of evidence on hazard potential. These include, but are not limited to: molecular weight, size, and shape; physical state (gas, liquid, solid); water or lipid solubility that can influence retention and tissue distribution; and potential for chemical degradation or stabilization in the body.

Interaction with cellular components and reactivity with macromolecules is a second major area covered. Factors such as molecular size and shape, electrophilicity, and charge distribution are analyzed to decide whether they would facilitate such reactions by the agent.

2.6.2. Structure-Activity Relationships

The role of structure-activity relationship (SAR) analysis in the assessment of the carcinogenic risk of an agent in question is dependent upon the availability and the quality of the toxicological data on the agent. For chemicals with data from reasonably conducted studies, SAR analysis is useful in providing input to determine the probable mechanism of action, which is important for hazard identification and for decisions on the appropriate methodology for quantitative risk assessment. For chemicals with either unsatisfactory or inadequate carcinogenicity data, SAR analysis may be used to generate, bolster, or mitigate the carcinogenic concern for the chemical, depending on the strength of and confidence in the SAR analysis. In addition, SAR analysis can also serve as a guide to evaluate carcinogenic potential of untested chemicals.

Currently, SAR analysis is most useful for chemicals that are believed to produce carcinogenesis, at least initially, through covalent interaction with DNA (i.e., DNA-reactive mutagenic electrophilic or proelectrophilic chemicals) (Ashby and Tennant, 1991; Woo and Arcos, 1989). In analyzing the SAR of DNA-reactive mutagenic chemicals, the following parameters should be considered (Woo and Arcos, 1989):

a. the nature and reactivity of the electrophilic moiety or moieties present;
b. the potential to form electrophilic reactive intermediate(s) through chemical, photochemical; or metabolic activation;
c. the contribution of the carrier molecule to which the electrophilic moiety (ies) is attached;
d. physicochemical properties (e.g., physical state, solubility, octanol-water partition coefficient, half-life in aqueous solution);
e. structural and substructural features (e.g., electronic, stearic, molecular geometric);
f. metabolic pattern (e.g., metabolic pathways and activation and detoxification ratio); and
g. the possible exposure route(s) of the subject chemical.

Following compliation of a carcinogenicity database for structural analogs, the above parameters are used to compare and place the subject chemical as to its carcinogenic potential among its analogs or congeners. In addition, the analysis is supplemented with any available information on the pertinent toxic effects of the compound, its potential metabolites, and its structural analogs. The

pertinent toxic effects are those known to contribute to carcinogenesis such as immune suppression or mutagenicity.

Suitable SAR analysis of non-DNA-reactive chemicals and of DNA-reactive chemicals that do not appear to bind covalently to DNA requires knowledge or postulation of the most probable causative mechanism(s) of action (e.g., receptor-mediated, cytotoxicity related) of closely related carcinogenic structural analogs. Examination of the physicochemical and biochemical properties of the subject chemical may then allow one to assess the likelihood that such a mechanism also may be applicable to the chemical in question and to determine the feasibility of conducting SAR analysis based on the mechanism.

2.6.3. Metabolism and Pharmacokinetics

Studies of the absorption, distribution, biotransformation and excretion of agents are used to make comparisons among species to assist in determining the implications of animal responses for human hazard assessment, to support identification of toxicologically active metabolites, to identify changes in distribution and metabolic pathway or pathways over a dose range and between species, and to make comparisons among different routes of exposure.

In the absence of data to compare species, it is necessary to assume that pharmacokinetic and metabolic processes are qualitatively comparable. If data are available (e.g., blood/tissue partition coefficients and pertinent physiological parameters of the species of interest), physiologically based pharmacokinetic models can be constructed to assist in determination of tissue dosimetry, species-to-species extrapolation of dose, and route-to-route extrapolation (Connolly and Andersen, 1991).

Analyses of adequate metabolism and pharmacokinetic data can be applied toward the following as data permit. Confidence in conclusions is greatest when in vivo data are available.

a. Identifying metabolites and reactive intermediates of metabolism and determining whether one or more of these intermediates are likely to be responsible for the observed effects. This information on the reactive intermediates will support and appropriately focus SAR analysis, analysis of potential mechanisms of action, and, in conjunction with physiologically based pharmacokinetic models, estimation of tissue dose in risk assessment (D'Souza et al., 1987; Krewski el al., 1987).
b. Identifying and comparing the relative activities of relevant metabolic pathways in animals with those in humans. This analysis can give insight on whether extrapolation of results of animal studies to humans will produce useful results.
c. Describing anticipated distribution within the body, and possibly identifying target organs. Use of water solubility, molecular weight, and

structure analysis can support inferences about anticipated qualitative distribution and excretion. In addition, describing whether the agent or metabolite of concern will be excreted rapidly or slowly or will be stored in a particular tissue or tissues to be mobilized later can identify issues in comparing species and formulating dose-response assessment approaches.

d. Identifying changes in pharmacokinetics and a metabolic pathway or pathways with increases in dose. These changes may result in the formation and accumulation of toxic products following saturation of detoxification enzymes. These studies have an important role in providing a rationale for dose selection in carcinogenicity studies. In addition, these studies may be important in estimating a dose over a range of high to low exposure for the purpose of dose-response assessment.

e. Determining the bioavailability of different routes of entry by analyzing uptake processes under various exposure conditions. This analysis supports identification of hazard for untested routes of entry. In addition, use of physicochemical data (e.g., octanol-water partition coefficient information) can support an inference about the likelihood of dermal absorption (Flynn, 1990).

In all of the above-listed areas of inquiry, attempts are made to clarify and describe as much as possible the variability to be expected because of differences in species, sex, age, and route of entry. Utilization of pharmacokinetic information takes into account that there may be subpopulations of individuals who are particularly vulnerable to the effects of an agent because of metabolic deficits or pharmacokinetic or metabolic differences (genetically or environmentally determined) from the rest of the population.

2.6.4. Mechanistic Information

{The material in this section is only a start. Substance-specific risk assessments may have little or no data in this category. Even when data are available, there is no standard for what is acceptable or what to expect. If there are no data, we will have to use default assumptions. How much information is enough is difficult to say until testing in this area is more regular.}

"Knowledge of carcinogenic mechanisms is incomplete in all cases. Information on how particular agents are likely to cause cancer may, however, be useful for appreciating more accurately the hazard that such agents pose to humans" (IARC, 1991). Results from short-term toxicological tests and molecular and cellular mechanistic studies are also useful in the interpretation of epidemiological and rodent chronic bioassay data used in hazard identification and characterization. These data may provide guidance for dose-response modelling.

Testing for tumorigenicity is usually done in long-term assays that involve exposure for much of an animal's lifespan.

Data from the long-term animal studies and the toxicity studies preceding them (e.g., evidence of lesion progression, or lack of progression, and hyperplasia at the same site as the neoplasia) may suggest a line of inquiry for further study. Cell necrosis is often an early finding (e.g., 20-90 days) and provides indirect evidence for subsequent tissue regeneration and compensatory growth mechanisms when these events are not directly observed. Other early changes observed during pre-chronic studies range from biochemical changes to altered hormone levels to organ enlargement (hyperplasia) to specific and marked histopathological changes (Hildebrand et al., 1991).

Conventional animal cancer bioassays provide little information on mechanism of action. Short-term animal assays generally have more defined study designs to provide information about potential mechanisms of action. A large number of short-term assays examine biological activities relevant to the carcinogenic process (e.g., mutagenesis, tumor promotion, aberrant intercellular communication, increased cell proliferation, malignant conversion, immunosuppression). In the future, mechanistic-based end points should play an increasing, and perhaps major, role in the assessment of cancer risk.

2.6.4.1. Genetic Toxicity Tests

Information on genetic damaging events induced by an agent is revealing about the possible mechanism of action of a carcinogen. Although the effectiveness of genetic toxicology tests in predicting cancer has been questioned (Brockman and DeMarini, 1988), the ability of these tests to detect mutagenic carcinogens has not been seriously challenged (Brockman and DeMarini, 1988; Prival and Dunkel, 1989; Tennant and Zeiger, 1992; Shelby et al., 1992; Jackson et al., 1992).

Recent studies on oncogenes provide evidence for the linkage between mutation and cancer (Bishop, 1991); activation of protooncogenes to oncogenes can be triggered, for example, by point mutations, DNA insertions, or chromosomal translocation (Bishop, 1991). In addition, the inactivation of tumor suppressor genes (anti-oncogenes) can occur by chromosomal deletion or aneuploidy (chromosome loss), and mitotic recombination (Bishop, 1989; Varmus, 1989; Stanbridge and Vavenee, 1989).

Genetic toxicology tests have been described in various reviews (Brusick, 1990; Hoffman, 1991). The EPA has published various testing requirements and guidelines for detection of mutagenicity (USEPA, 1991a). A useful method to "portray" data graphically, and which provides a reasonable starting point for analysis, is the genetic activity profile (GAP) methodology developed by the USEPA (Garrett et al., 1984; Waters et al., 1988).

Many test systems have been developed to assay agents for their mutagenic

potential.[3] These include assays for changes in DNA base pairs of a gene (i.e., gene mutations) and microscopically visible changes in chromosome structure or number. Structural aberrations include deficiencies, duplications, insertions, inversions, and traslocation. Other assays that do not measure gene mutations or chromosomal aberrations per se provide some information on an agent's DNA damaging potential (e.g., tests for DNA adducts, strand breaks, repair, or recombination).

Distinguishing a carcinogenic agent as a mutagen or nonmutagen is an important decision point in defining the mechanism of action. To designate a putative carcinogen as a mutagen, there should be confidence that the primary target is DNA. Mutagenic end points that involve stable changes in DNA structure are emphasized because of their relevance to carcinogenesis. These include gene mutations and chromosomal aberrations.

To be of value in cancer risk assessment, genetic toxicology data must meet the demands of scientific scrutiny. A higher level of confidence that a carcinogen is a mutagen is assigned to agents that consistently induce direct structural changes in DNA in a number of test systems. Although important information can be gained from in vitro assays, a higher level of confidence is given to a data set that includes in vivo evidence. In vivo data is emphasized because many agents require metabolic conversion to an active intermediate for biological activity. Metabolic activation systems can be incorporated into in vitro assay; however, they do not always mimic mammalian metabolism perfectly. If available, human genetic toxicity end points relevant to carcinogenesis are important in vivo data.

It is not possible to illustrate all potential combinations of evidence, and considerable judgment must be exercised in reaching conclusion. Certain responses in tests that measure DNA damaging potential (e.g., DNA repair activity, adducts or strand breakage in DNA) other than gene mutations and chromosomal aberrations may provide a basis for raising the level of confidence in designating a carcinogen as mutagenic.

There are many other mechanisms by which agents cause genetic damage secondary to other effects. For example, an agent might interfere with DNA repair or possibly increase DNA damage through an increase in oxidative radical production (Cerutti et al., 1990). Reliance on evidence for induced gene mutations or chromosomal aberrations to define a mutagenic carcinogen is not meant to downplay the importance of these secondary mechanisms or other genetic end points.

Aneuploidy (i.e, a change in chromosome number) may play an important role in the development of some tumors (Kondo et al., 1984; Cavenee et al., 1983; Barrett et al., 1985), but it may result from interactions with cellular components

[3] Ability to induce heritable or stable alterations in DNA structure and content.

(e.g., mitotic apparatus) other than with DNA. For this reason, aneuploidy is not considered evidence for designating a carcinogen as mutagenic. Aneuploidy is important information regarding potential carcinogenicity by other genetic mechanisms and should be factored into the evaluation concerning mechanisms of action.

Because mutagenic carcinogens have been observed to induce tumors across species and at multiple sites, evidence of both mutagenicity and tumor responses in multiple species or sexes significantly increases concern for the human carcinogenic potential of an agent. Absence of mutagenicity in multiple test systems gives insight into alternative mechanisms by which non-mutagenic carcinogens may act. The consideration of alternative non-mutagenic mechanisms does not necessarily provide a basis for discounting positive results in the animal cancer bioassay and thus does not negate the concern for human risk. On the other hand, evidence for non-mutagenicity and the lack of responses in a chronic rodent bioassay increases the confidence that an agent is not a human hazard.

2.6.4.2. Other Short-Term Tests

In addition to genetic toxicity tests, information on increased cell proliferation, cell transformation, aberrant intercellular communication, receptor mediated effects, changes in gene transcription (i.e., events that involve a change in the function of the genome) can provide useful information in the evaluation of mechanism of action and insight into the carcinogenic potential of an agent. It is not possible to describe all the data that might be encountered in a substance-specific assessment. Thus, the most conventional ones or those that are currently emphasized are mentioned as examples.

Cell proliferation plays a key role at each stage in the carcinogenic process and it is well established that increased rates of cell proliferation are associated with increased cancer risk. This increased risk is due to the increased susceptibility of proliferating cells to both spontaneous genetic damage as well as that induced by mutagens. Therefore, mitogenic activity in a mutagenic agent could be expected to further increase the probability of mutagenesis and, therefore, carcinogenesis. Cell proliferation or mutation alone are insufficient to cause neoplasia; further events are required for cells to escape from growth control, to attain the ability to grow independently, and to acquire invasiveness.

Evidence for the increased rate of cell division may be determined by measuring the mitotic index, or by supplying a specific DNA precursor to the cell (e.g., ^{3}H-thymidine or bromodeoxyuridine) and counting the percentage of cells that have incorporated the precursor into the replicating DNA, or by immunodetection of proliferation-specific antigens. These analyses are carried out in vitro, during pre-chronic studies, or as part of the long-term animal cancer bioassay.

Non-mutagenic carcinogens are more likely than mutagenic carcinogens to affect a specific sex or organ. Stable cell populations with a potential for a high

rate of cell replication are more often affected than cell populations with a naturally high rate of replication. These properties have been used to develop two stage initiation-promotion studies based on preneoplastic lesions or tumors of the mammary gland, urinary bladder, forestomach, thyroid, kidney, and liver. Such tests provide mechanistic insight as well as supportive evidence for carcinogenicity (Drinkwater, 1990).

Several short-term tests respond to both mutagenic and non-mutagenic carcinogens. Assays for measuring perturbation of gap-junctional intercellular communication may provide and indication of carcinogenicity, especially promotional activity, and provide mechanistic information (Yamasaki, 1990). Cell transformation assays have been widely used for studying mechanistic aspects of chemical carcinogenesis because in vitro cell transformation is considered to be relevant to the in vivo carcinogenic process.

2.6.4.3. Short-Term Assays for Carcinogenesis

In addition to more conventional long-term animal studies, other shorter-term animal models can yield useful information about the carcinogenicity of agents. Some of the more common tests include mouse skin (Ingram and Grasso, 1991), transplacental and neonatal carcinogenesis (Ito, 1989), mammary gland tumor studies and preneoplastic lesions or altered cell foci (e.g., in liver, kidney, pancreas). Currently, increased research emphasis is being put on alternative approaches to the chronic rodent cancer bioassay. As an example, significant progress is being made using fish models (Bailey et al., 1984; Couch and Harshbarger, 1985).

2.6.4.4. Evaluation of Mechanistic Studies

The entire range of data about an agent's physical-chemical properties, structure-activity relationships to carcinogenic agents, and biological activity in vitro and in vivo is reviewed for mechanistic insights. The weight and significance of the observation of carcinogenic activity of the agent in vivo can be greatly influenced by the available data in several areas, all of which should be considered. Discussion should summarize available data on the agent's effects on DNA structure or expression and its effects on the cell cycle. Types of information to be considered include: whether the agent is a mutagenic or a non-mutagenic carcinogen, specific effects on proto-oncogenes or tumor suppressor genes and DNA transcription, and structural or functional analogies to agents with the above effects.

Information demonstrating effects on the cell cycle would include: mitogenesis, effects on differentiation, effects on cell death (apoptosis), tissue damage resulting in compensatory cell proliferation, receptor-mediated effects on growth

signal transduction, and structural or functional analogies to agents with the above effects.

Information demonstrating effects on cell interaction might include: effects on contact inhibition of growth, intracellular communication, or immune reactions, and structural or functional analogies to agents with these effects.

These are not intended to be exclusive of other pertinent data not specifically listed. In addition, available data on the comparative pharmacokinetics and metabolism of the agent in animals and humans is assessed to consider whether similar mechanisms of action may be operating in humans and animals. (A similar summarization of evidence has been reported by IARC, 1991).

In evaluating carcinogenic potential and mechanism of action, analyses and conclusions based on short-term tests are accompanied by a discussion of the level of confidence that can be applied to all the data. The level of confidence is based on the following (not necessarily exclusive) factors: (a) the spectrum of endpoints relevant to carcinogenesis and the number of studies used for detecting each end point and consistency of the results obtained in different test systems and different species, (b) in vivo as well as in vitro observations, (c) the consistency and concordance of test results, (d) reproducibility of the results within a test system, (e) existence of a dose-response relationship, and (f) whether the tests are conducted in accordance with appropriate protocols agreed upon by experts in the field. For, example, a high level of confidence in describing the potential influence of an agent on carcinogenic events is based on results covering a number of events relevant to stages of carcinogenesis, a number of studies including in vivo tests showing consistent trends and good concordance. A low confidence data set is one that was sparse or has incongruous results and no clear data trends.

The strength of an hypothesis about mechanism of action generated by analysis of data in the above areas should be described by the following criteria:

a. The operation of the mechanism in carcinogenesis must have been explained by a body of research data and have been generally accepted in the scientific community as a mechanism of carcinogenesis;
b. There must be a body of experimental data that show how the agent in question participates in the mechanism of action. In the absence of data about the mechanism of action of an agent, decisions are made using default assumptions:
c. That animal effects are relevant to human effects; and
e. That the agent affects carcinogenesis with dose and response relating linearly at low exposure.

Both of these science policy assumptions are supported by current knowledge of carcinogenic processes, in the absence of better data. Each assumption must be examined in substance-specific risk assessments and replaced or joined by alternative analysis when adequate scientific data exist.

2.7. Summary Of Experimental Evidence

{Criteria and examples for categorization of experimental evidence are major issues, particularly the weight of evidence contribution of research data of new kinds of genes and signal transduction pathways of growth control.}

A summary is made of all the experimental evidence that is relevant to human carcinogenic potential.

The confidence of an agent is potentially carcinogenic for humans increases as the number of animal species, strains, or number of experiments and doses showing a carcinogenic response increases. It also increases as the number of tissue sites affected by the agent increases and as the time to tumor occurrence or time to death with tumor decreases in dose-related fashion. Confidence also increases as the proportion of tumors that are malignant increases with dose and if the observed tumor types are historically rare in the species.

{The appropriate use of molecular biological data in the overall weight of evidence is a question. The strength of inferences to be drawn from data such as tumor susceptibility or gene effects is an unsettled issue.}

The weight of other experimental evidence increases or decreases the weight of findings relevant to human hazard in the following ways listed below. Findings in vivo add to the weight of evidence more rapidly than in vitro findings.

- physical-chemical properties and structural or functional analogies can support inferences of potential carcinogenicity;
- results in a number of short-term studies that are consistent can support inferences about potential human effects;
- evidence of mutagenic effects on proto-oncogenes or tumor suppressor genes;
- evidence of effects on cell growth signal transduction affecting cell division, differentiation; or cell death; and
- induction of neoplastic behavioral characteristics in cells in culture or in vivo.

The summarization of experimental evidence refers only to the weight of evidence that an agent may or may not be carcinogenic in humans, not the dose-response relationship, which is the subject of a separate analysis.

The following four categories are used to summarize all of the experimental data relevant to inferences about human carcinogenic potential of an agent. Tumor responses that the Agency has found to be not relevant for inferring human hazard are not given weight. Other responses whose relevance is unresolved are noted in the categorization of evidence. Categorization is a matter of scientific

judgment, and the descriptions below are to be used as guidance in making that judgment, not as absolute criteria.

2.7.1. Category 1

The following examples illustrate persuasive evidence of carcinogenic potential. Other combinations of data also may be persuasive. In prospect, continued research on the role of agents in mutations of proto-oncogenes and tumor suppressor genes and related research on receptor-mediated effects on growth control genes also may provide persuasive data.

Examples:

1. Long-term animal experiments showing increased malignant and benign tumors

a. when the increased incidence of tumors is in more than one species or in more than one experiment (i.e., results are complicated with different routes of administration, or affect a range of dose levels)

- at multiple sites, or
- at a limited number of sites with a supporting weight of evidence from structure-activity analysis, or available short-term tests;

b. when there is a response to an unusual degree in a single experiment with regard to high incidence of a low-incidence background tumor, unusual site or type of tumor, or early age at onset

- with a dose-related increase in a highly malignant tumor or in early death with cancer, or
- with a supporting weight of evidence from structure activity analysis or from available short-term studies; or

c. in more than one experiment, at a single site

- with a highly supportive weight of evidence from SAR analysis and numerous consistent findings of effects on carcinogenic processes in short-term studies, or
- with a dose-related increase in tumor malignancy.

2. Evidence that an agent is readily converted to a metabolite for which independent human or animal evidence is categorized as Group 1 and data are supportive of like pharmacokinetic disposition, or short-term studies of the agent are comparable in result with those of the metabolite.
3. Short-term experiments that demonstrate an agent's influence on carcinogenic processes in vivo consistent with in vitro studies, SAR, and physical-chemical properties that are highly supportive of carcinogen activity. These are supported

by studies showing comparable metabolism and pharmacokinetics between study species and humans.

2.7.2. Category 2

Examples for this category include:

1. A long-term animal experiment or experiments showing increased incidence of malignant tumors or combined malignant and benign tumors that falls short of the weight for categorization as Category 1.
2. Evidence that an agent is readily converted to a metabolite for which independent human or animal evidence is Category 2 and data are supportive of like pharmacokinetic disposition, or short-term studies of the agent are comparable in result with those of the metabolite.
3. Short-term studies and other evidence as described in 2.6.4.4. together with data supporting the likelihood of comparability in metabolism and pharmacokinetics between species.

2.7.3. Category 3

The experimental evidence does not support a conclusion either way about potential carcinogenicity because:

- too few data are available;
- evidence is limited to tumorigenicity and is found *solely* in studies in which the manner of administration (e.g., injection) or other aspects of study protocol present difficulties of interpretation; or
- evidence of carcinogenicity is found at a single animal site in one species and sex in one or more experiments; the response is weak and without characteristics that give weight to a conclusion about potential human carcinogenicity.

For example, data are inconclusive if experimental data apart from the animal response do not support any positive inference about the agent's carcinogenic potential and if the animal response has a consistent pattern of most of the following characteristics:

- At least two species have been tested, and the tumor response is seen only at the highest dose, in one sex, and one species.
- The tumor incidence is predominantly benign and is seen only in one target organ.
- The tumor is recognized as a common tumor type in that species, strain, and sex. In addition, the observed tumor rate, although statistically

significant in the experiment, is at or near the upper range of the historical control incidence.

- The tumors do not cause death in the affected animals during the duration of the study and do not appear sooner in the treated animals than in the controls.

Such evidence may add some weight to results of the human studies.

2.7.4. Category 4

This summarization would apply when no increased incidence of neoplasms has been observed in at least two well-designed and well-conducted animal studies in different species including both sexes. The exposures are specified and the implication is that either the agent is not carcinogenic or the studies had insufficient power to detect an effect.

2.8. Human Hazard Characterization

Evidence from all of the elements of hazard assessment are drawn together for an overall characterization of potential human hazard as indicated in Figure 1.

2.8.1. Purpose and Content of Characterization

The major lines of observational human evidence and experimental evidence and reasoning are clearly described. Major judgments made in the face of conflicting data are particularly highlighted and explained, as are the assumptions or inferences made to address gaps in information. The strengths and weaknesses of the available data are described and related to resulting confidence in the characterization. The hazard characterization addresses not only the question of carcinogenic properties, but also, as data permit, the question of the conditions (dose, duration, route) under which these properties may be expressed.

To provide a basis for combining hazard and environmental exposure data in the final risk characterization, the hazard characterization points to differences expected according to route of exposure, if such differences can be determined. The assumption is made that the hazard is not route-specific, if this is reasonable and not contradicted by existing data. Information about the plausible mechanism or mechanisms of action is characterized and its implications for dose-response assessment are explained, including conditions of dose and duration.

2.8.2. Weight of Evidence for Human Carcinogenicity

{NOTE TO THE READER: The question as to whether to abandon our alphanumerical

system entirely or merge it with a narrative statement has not been decided. We may retain labels of A, B, C, etc., labels for weight of evidence groups.}

A brief narrative statement is used to summarize the weight of evidence. It incorporates judgment about data from all elements of hazard assessment. A summary statement cannot resolve data interpretation issues; it can only focus judgments and help convey them. The purpose is to give the risk manager a sense of the evidence and of the risk assessor's confidence in the data and their interpretation for the assessment of human carcinogenicity potential and to allow comparison of weight of evidence judgments from case to case. A weight of evidence conclusion incorporates judgments both about overall confidence in a set of data as a basis for drawing conclusions and about the consistency and congruence of inferences supported by the set of data.

A weight of evidence conclusion is based both observational data from human studies and experimental data. All of the elements of analysis included in hazard assessment form the basis of judgment. The summarizations of experimental evidence and human evidence are ingredients for a weight of evidence statement. Note that animal tumor responses that the Agency considers not relevant for inferring human hazard are not weighed. However, unresolved questions about relevance are all noted and considered in the statement.

As the first step, a decision is made on whether the evidence is adequate or not adequate for characterization. "Not adequate" means that the existing data are inadequate overall to support a conclusion because either there are too few data or the data are flawed due to experimental design or conduct, or because findings are not substantial enough to support inferences either way about potential human carcinogenicity. Typically, human or experimental data that are in Category 3 would be considered as not adequate for characterization.

If the evidence is adequate for a weight-of-evidence determination, it is described within a narrative statement. The narrative statement explains the weight of evidence by summarizing the content and contribution of individual lines of evidence and explaining how they combine to form the overall weight of evidence. The statement highlights the quality and extent of data and the congruence, or lack of congruence, of inferences they support. The statement also highlights default assumptions used to address gaps in knowledge.

The statement gives the weight of evidence by route of exposure, pointing out the basis of anticipated differences and whether the default assumption supporting extrapolation of hazard potential between routes has been used and is appropriate. Anticipated potency differences by route are pointed out, based on comparatively poor to ready absorption by different routes (see § 2.6.3. Metabolism and Pharmacokinetics).

The statement discusses the data implications for mechanism of action. It recommends a general approach or approaches for dose-response assessment in

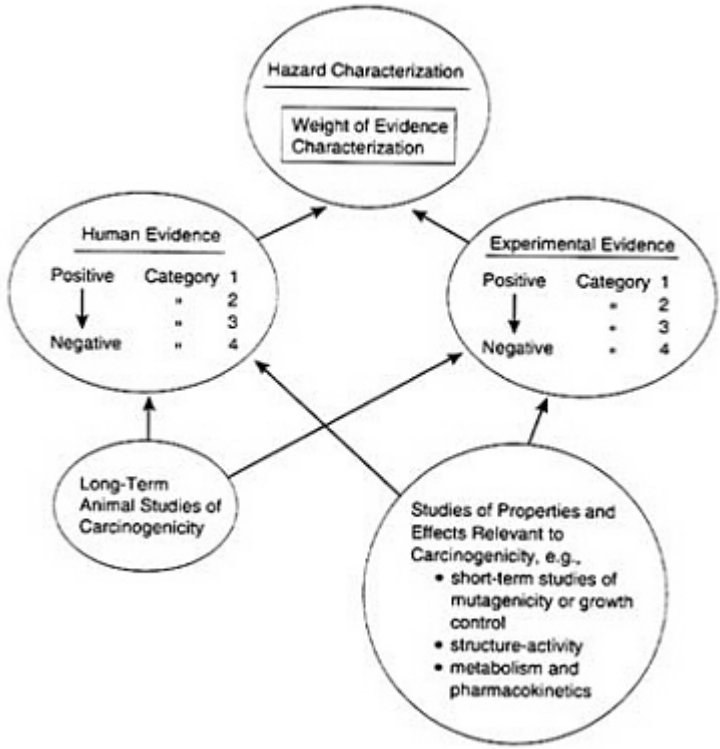

FIGURE 1

accordance with what the hazard data imply about the nature of dose-response below the range of observation of available studies. A weight of evidence for hazard by any mechanism is characterized. Thus, for example, an agent that is estrogenic and not likely to cause permanent genetic changes is characterized as a carcinogenic hazard, with any limitations of dose being explained in the narrative statement. The quantitative dose-response estimation or shape of the dose-response curve does not affect the weight of evidence for hazard.

The statement notes whether its source is an individual EPA office or an EPA consensus. The overall conclusion is noted by use of one of the following descriptors: **"known," highly likely,"** or **"likely"** to be a human carcinogen; **"some evidence"** or **"not likely to be a human carcinogen at exposure levels studied or alternately under conditions of environmental exposure."** These descriptors fall along a continuum of likelihood that an agent has human carcinogenic potential. More than one descriptor may apply to a single agent if the weight of evidence differs by route of administration. Also, two descriptors may

be applied if the evidence for a route is judged to fall between two descriptors. These standard descriptors are provided for the purpose of maintaining consistency of expression of conclusions from case to case. The text of the narrative statement as a whole is the primary means of conveying information on the weight of evidence.

2.8.2.1. Descriptors

{The number of descriptor categories for total weight of evidence is a continuing issue. The evidence is along a continuum. How many descriptors are needed to represent the continuum? What are the criteria for establishing them?}

Explanations of the general levels of evidence associated with descriptors in terms of the summarizations of evidence made in the course of a hazard assessment are as follows:

"Known" to be carcinogenic in humans is a statement that evidence is convincing (Category 1) that the agent has observed carcinogenic effects in humans by a specified route or routes of exposure.

"Highly likely" is a statement that:

1. there is persuasive experimental evidence of carcinogenicity (Category 1) and suggestive human evidence (Category 2), or
2. there is persuasive experimental evidence (Category 1) showing a very strong animal response (multiple tumor sites in more than one species), or
3. an agent is known to be a carcinogen in humans by one route of exposure (known) is also absorbed by another route, making carcinogenic effects "highly likely" by the second route.

"Likely" is a statement that:

1. there is persuasive experimental evidence (Category 1), or
2. there is suggestive evidence from human data (Category 2) with experimental evidence (Category 2) that supports the likelihood that the human effects seen were due to the agent in question.

"Some evidence" is a statement that:

1. there is experimental evidence (Category 2), or
2. suggestive human evidence (Category 2).

However, the totality of the evidence is weak because findings are inconsistent, or there are many gaps in the data.

"Not likely to be a human carcinogenic at exposure levels studied or alternately, under conditions of environmental exposure" is a statement that:

1. human evidence has been summarized as no evidence at exposure levels studied (Category 4), and there are no positive animal findings, or
2. experimental evidence has been summarized as no evidence at exposure levels studied (Category 4), and there are no positive human findings, or
3. the occurrence of carcinogenic effects is not expected for a particular route of human environmental exposure (oral, dermal, inhalation) because the agent is not absorbed by that route, or
4. the mechanism of carcinogenicity of an agent operates only at doses above the range of plausible environmental exposure, e.g., carcinogenesis as a secondary effect of another effect that occurs only at high doses, or
5. the occurrence of carcinogenic effects depends on administration of the agent in a manner that has no parallel with plausible environmental exposure, e.g., injection of polymers.

This descriptor is explained in the narrative statement as being applicable only to the specific exposure levels studied or environmental exposure conditions which are given in the statement.

2.8.2.2. Examples of Narrative Statements

Compound X

Following review of all available data relevant to the potential human carcinogenic hazard of X (CAS # 000001), the … Office of EPA concludes that X is not likely to be carcinogenic to humans by any route of exposure at environmental levels. This determination is based on experimental evidence. No human studies on X are available for evaluation. The evidence supporting this finding is the animal response.

With dietary administration, X caused a statistically significant increase in the incidence of urinary bladder hyperplasia and tumors (urinary bladder transitional cell papillomas and carcinomas) in male but not in female Charles River CD rats at high dose levels (>;30,000 ppm). The tumors were seen only at dose levels producing calculi in the kidneys, ureters and the urinary bladder. The presence of the urinary bladder calculi was associated with a decrease in the urinary pH. The urinary bladder calculi were almost always associated with urinary bladder hyperplasia (>;90%). A major metabolite of X did not cause any increase

in tumor incidence in another bioassay in rats. X was not carcinogenic in mice in well-conducted experiments.

The in vivo (mouse micronucleus test) and in vitro (in bacteria and yeast) short term- studies on X indicate with medium confidence that X is not genotoxic. Structure-activity relationship analysis reveals no chemicals which are related to X and also induce tumors. It is concluded that the tumor response in male rats was secondary to stone formation at high doses, and may be a phenomenon unique to the male rats. No dose-response analysis is recommended unless a high-dose environmental exposure to humans is discovered.

Compound Y

Following review of all available data relevant to the potential human carcinogenic hazard of Y (CAS # 000002), EPA concludes that Y is likely to be carcinogenic to humans by all routes of exposure. This determination is based on experimental evidence. No human studies are available for evaluation. The strongest lines of evidence supporting findings on Y are animal experiments and structure-activity relationships.

Rodent studies showed statistically significant increases in the incidence of liver tumors (hepatocellular adenomas and carcinomas combined) in two strains of mice, in two independent and adequately conducted studies. The increases of liver tumors occurred at high and low doses. Y also produced a statistically significant increase in stomach tumors (papillomas) in both male and female mice at a dose also producing significant mortality and reduced body weight (-18% to -23% throughout the study) and the presence of white foci and ulcers in the stomach of occasional animals.

Y, administered orally, did not induce tumors in F344 rats in an adequately conducted study. Data from acute inhalation toxicity and dermal absorption studies show that Y is absorbed by both dermal and inhalation exposure.

Y caused gene mutations and chromosome aberrations in *D. melanogaster* and DNA damage in yeast, but it did not induce mutagenic effects in either in vitro or in vivo mammalian systems. The mutagenicity data set is of low confidence, and it neither supports nor contradicts inferences about carcinogenicity. In addition, it does not suggest a mechanism of action.

Structure-activity relationship analysis shows that Y is very closely related

in structure to eight other chemicals, all of which produce liver tumors in mice, rats, or both.

Based upon the above analysis, it is suggested that the dose-response analysis employ a default assumption of linearity at low dose and consider the liver tumor in mice as an appropriate endpoint.

3. Dose-Response Assessment

3.1. Purpose And Scope Of Dose-Response Assessment

Dose-response assessment tests the hypothesis that an agent has produced an effect and portrays the relationship between the agent and the response elicited. In risk assessments, dose and response observations from experimental or epidemiological studies are often projected to much lower exposure levels encountered in the environment.[4] In addition, the mathematical models used for extrapolation are based on general assumptions about the nature of the carcinogenic process. These assumptions may be untested for the particular agent being evaluated (Kodell, in press). If the dose-response relationship is developed from an experimental animal study, it also must be extrapolated from animals to humans. Because of these inherent uncertainties, projections well outside the range of the observed data are treated as bounding estimates, not as true values. Information that shows a comparable pharmacokinetic and metabolic response to an agent in humans and animals greatly increases confidence in the dose-response analysis. Data suggesting that an agent works through a common mechanism of action in humans and animals also greatly increases confidence in the low dose extrapolation. In the absence of such data, default approaches provide upper-bound estimates of response at low doses, with a lower limit as small as zero at very low doses.

In the absence of dose-response data on members of a class of agents, it may be possible to construct a set of toxicity equivalence factors (TEF) to be used to

[4] For this discussion, "exposure" means contact of an agent with the outer boundary of an organism. "Applied dose" means the amount of an agent presented to an absorption barrier and available for absorption; "internal dose" means the amount crossing an absorption barrier (e.g., the exchange boundaries of skin, lung, and digestive tract) through uptake processes; and the amount available for interaction with an organ or cell is the "delivered dose" for that organ or cell. For more detailed discussion see Exposure Assessment Guidelines __ FR ___ (1992).

quantify dose-response by reference to an already-characterized member of the class.

3.2. Elements of Dose-Response Assessment

The elements of dose response analysis include selection of response data and dose data, followed by a stepwise dose-response analysis. The first step in the dose-response analysis is fitting of the data in the range of study observation; the second step, if needed, is extrapolation of the dose-response relationship to the range of the human exposure of interest.

A dose-response assessment should take advantage of available data to support a more confident analysis. When data gaps exist, assumptions based on current knowledge about the biological events in carcinogenesis and pharmacokinetic processes are used.

3.2.1. Response Data

Appropriate response data, as well as mechanistic information from the hazard characterization, are applied in the dose-response assessment. The quality of the data and their relevance to human exposure are important selection considerations.

If adequate positive human epidemiologic data are available, they are usually the preferred basis for analysis. Positive data are analyzed to estimate response to environmental exposure in the observed range. (USEPA, 1992a). Extrapolation to lower environmental exposure ranges is carried out, as needed. If adequate exposure data exist in a well-designed and well-conducted epidemiologic study that detects no effects, it may be possible to obtain an upper-bound estimate of the potential risk. Animal-based estimates, if available, are also presented, and the animal results are compared with the upper-bound estimate from human data for consistency.

When animal studies are used, response data from a species that responds most like humans should be used, if information to this effect exists. When an agent was tested in several experiments involving different animal species, strains, and sexes at several doses and different routes of exposure, the following approach to selecting the data sets is generally used:

a. The tumor incidence data are separated into data sets according to organ site and tumor type.
b. All biologically and statistically acceptable data sets are examined.
c. Data sets are analyzed with regard to route of exposure.
d. A judgment is reached based on biological criteria as to which set or sets best represents the body of data for the purpose of estimating human response. This judgment is augmented with judgment as to the statistical suitability of the data for modeling in the experimental data

range. The hazard characterization is the point of reference for the initial judgment. The following characteristics of a data set favor its selection.

- high quality of study protocol and execution;
- malignant neoplasms;
- earlier onset of neoplasm;
- greater number of data points to define the relationship of dose and response;
- background incidence in test animal is not unusually high;
- most sensitive-responding species are used; or
- data on a related effect (e.g., DNA adduct formation) or mechanistic data to augment the tumor.

Appropriate options for presenting results include use of a single data set, combining data from different experiments (Stiltler et al., 1992), showing a range of results from more than one data set, representing total response in a single experiment by combining animals with tumors or a combination of these options. The rationale for selecting an approach is presented, including the biological and statistical considerations involved. The objective is to provide a best judgment of how to represent the observed data.

Benign tumors are usually combined with malignant tumors for risk estimation if the benign tumors are considered to have the potential to progress to associated malignancies of the same histogenic origin. (McConnell, 1986). When tumors are thus combined, the contribution to the total risk of benign tumors is indicated. The issue of how to consider the contribution of the benign tumors should be discussed in the dose-response characterization and risk characterization.

Data on certain endpoints related to tumor induction may be used to extend dose-response analysis below the relatively high dose range in which tumors are observable. These data permit extension of the curve-fitting analysis (Swenberg et al., 1987) and may provide parameters for applying a mechanism-based model (US EPA Dioxin Assessment, 1992c). Data might include information on receptor binding, DNA adduct formation, physiological effects such as disruption of hormone activity, or agent-specific alterations in cell division rates. In considering whether such endpoints can be applied, key issues are confidence that the data reflect carcinogenic effects of the agent and that these have been well measured with a dose-effect trend.

3.2.2. Dose Data

Regardless of the source, animal experiments or epidemiologic studies, several questions need to be addressed in arriving at an appropriate measure of dose. One question is whether data are sufficient to estimate internal dose or delivered

dose. Part of this question is whether the parent compound, a metabolite, or both agents are closer in a metabolic pathway to a carcinogenic form.

The delivered dose to target is the preferred measure of dose. In practice, there may be little or no information on the concentration or identity of the active agent at a site of action; thus, being able to compare the applied and delivered doses between routes and species is an ideal that is rarely attained. Even so, incorporating data to the extent possible is desirable.

Even if pharmacokinetic and metabolic data are sufficient to derive a measure of delivered dose to the target, the dose-response relationship is also affected by kinetics of reactions at the target (pharmacodynamics) and by other steps in the development of neoplasia. With few exceptions, these processes are currently undefined.

The following discussion assumes that the analyst will have data of varying detail in different cases about pharmacokinetics and metabolism. Approaches to limited data are outlined as well as approaches and judgments for more sophisticated analysis based on additional data.

3.2.2.1. Base Case — Few Data

Where there are insufficient data available to define the equivalent delivered dose between species, it is assumed that delivered doses at target tissues are directly proportional to applied doses. This assumption rests on the similarities of mammalian anatomy, physiology, and biochemistry generally observed across species. This assumption is more appropriate at low applied dose concentrations where sources of nonlinearity, such as saturation or induction of enzyme activity, are less likely to occur.

The default procedure is to scale daily applied doses experienced for a lifetime in proportion to body weight raised to the 3/4 power ($W^{3/4}$). Equating exposure concentrations in parts per million units for air, food, or water is an alternative version of the same default procedure because daily intakes of these are in proportion to $W^{3/4}$. The rationale for this factor rests on the empirical observation that rates of physiological processes consistently tend to maintain proportionality with $W^{3/4}$. A more extensive discussion of the rationale and data supporting the Agency's adoption of this scaling factor can be found in (USEPA, 1992b).

The differences in biological processes among routes of exposure (oral, inhalation, dermal) can be great, due to, for example, first pass effects and differing results from different exposure patterns. There is no generally applicable method for accounting for these differences in uptake processes in quantitative route-to-route extrapolation of dose-response data in the absence of good data on the agent of interest. Therefore, route-to-route extrapolation of dose data will be based on a case-by-case analysis of available data. When good data on the agent itself are limited, an extrapolation analysis can be based on expectations from

physical chemical properties of the agent, properties and route-specific data on structurally analogous compounds, or in vitro or in vivo uptake data on the agent. Route-to-route uptake models may be applied if model parameters are suitable for the compound of interest. Such models are currently considered interim methods; further model development and validation is awaiting the development of more extensive data (see generally, Gerrity and Henny, 1990).

3.2.2.2. Pharmacokinetic Analyses

Physiologically based mathematical models are potentially the most comprehensive way to account for pharmacokinetic processes affecting dose. Models build on physiological compartmental modeling and attempt to incorporate the dynamics of tissue perfusion and the kinetics of enzymes involved in metabolism of an administered compound.

A comprehensive model requires the availability of empirical data on the carcinogenic activity contributed by parent compound and metabolite or metabolites and data by which to compare kinetics of metabolism and elimination between species. A discussion of issues of confidence accompanies presentation of model results (Monro, 1991). this includes considerations of model validation and sensitivity analysis that stress the predictive performance of the model. Another assumption made when a *delivered* dose measure is used in animal-to-human extrapolation of dose-response data is that the pharmacodynamics of the target tissue(s) will be the same in both species. This assumption should be discussed, and confidence in accepting it should be considered in presenting results.

Pharmacokinetic data can improve dose-response assessment by accounting for sources of change in proportionality of applied-to- internal dose or to delivered dose at various levels of applied dose. Many of the sources of potential nonlinearity involve saturation or induction of enzymatic processes at high doses. An analysis that accounts for nonlinearity (for instance, due to enzyme saturation kinetics) can assist in avoiding over estimation or under estimation of low dose if extrapolation is from a sublinear or supralinear part of the experimental dose-response curve. (Gillette, 1983). Pharmacokinetic processes tend to become linear at low doses, an expectation that is more robust than low-dose linearity of response (Hattis, 1990). Thus, accounting for nonlinearities allows better description of the shape of the curve at higher levels of dose, but cannot determine linearity or nonlinearity of *response* at low dose levels (Lutz, 1990; Swenberg et al., 1987).

3.2.2.3 Additional Considerations for Dose in Human Studies

The applied dose in a human study has uncertainties because of the exposure fluctuations that humans experience compared with the controlled exposures

received by animals on test. In a prospective cohort study, there is opportunity to monitor exposure and human activity patterns for a period of time that supports estimation of applied dose (USEPA, 1992a). In a retrospective cohort study, exposure is based on human activity patterns and levels reconstructed from historical data, contemporary data, or a combination of the two. Such reconstruction is accompanied by analysis of uncertainties considered with sensitivity analysis in the estimation of dose (Wyzga, 1988; USEPA, 1986). These uncertainties can also be assessed for any confounding factor, for which a quantitative adjustment of dose-response data is made (USEPA, 1984).

Exposure levels of groups of people in the study population often are represented by an average when they are actually in a range. The full range of data are analyzed and portrayed in the dose-response analysis when possible (USEPA, 1986).

The cumulative dose of an agent is commonly used when modeling human data. This can be done, as in animal studies, with a default assumption in the absence of data that support a different dose surrogate. Given data of sufficient quality, dose rate or peak exposure can be used as an alternative surrogate to cumulative dose.

3.3 Selection Of Quantitative Approach

Because risks at relatively low exposure levels generally cannot be measured directly either by animal experiments or by epidemiologic studies of reasonable sample size, a number of mathematical models have been developed to extrapolate from high to low dose. Different extrapolation models may fit the observed data reasonably well but may lead to large differences in the projected risk at lower doses. As was pointed out by OSTP (1985 see Principle 26), no single mathematical procedure is recognized as the most appropriate for low-dose extrapolation in carcinogenesis. Low-dose extrapolation procedures use either mechanistic or empirical models. When sufficient biological information exists to identify and describe a mechanism of action, low-dose extrapolation may be based on a mathematical representation of the mechanism. When the mechanism is unknown or information is limited, low-dose is derived from an empirical fit of a curve compatible with the available information.

If a carcinogenic agent acts by accelerating the same carcinogenic process that leads to the background occurrence of cancer, the added effect on the population at low doses marginally above background level is expected to be linear. Above background level, the population response may continue to be linear in the case of an agent acting directly on DNA, or the population response may be influenced by individual variability in sensitivity to phenomena such as disruption of hormone homeostasis or receptor-mediated activity. If the agent acts by a mechanism with no endogenous counterpart, a population response threshold may exist (Crump et al., 1976; Peto, 1978; Hoel, 1980; Lutz, 1990). The

Agency reviews each assessment as to the evidence on carcinogenesis mechanisms and other biological or statistical evidence that indicates the suitability of a particular extrapolation model. When longitudinal data on tumor development are available, time-to-tumor or survival models may be used and are preferred. In all cases, a rationale is included to justify the use of the chosen model.

The goal in choosing an approach is to achieve the closest possible correspondence between the approach and the view of the agent's mechanism of action developed in the hazard assessment. If the hazard assessment describes more than one mechanism as plausible and persuasive given the data available, corresponding alternative approaches for dose-response analysis are considered.

3.3.1. Analysis in the Range of Observation

In portraying dose response in the range of observed data, analyses incorporate as much reliable information as possible. Pharmacokinetic data or interspecies scaling is used to derive human-equivalent measures of the animal-administered dose. The empirical response data analyzed include tumor incidence data augmented, if possible, by incidence data on effects leading to the tumor response, e.g., DNA adduct or other effect-marker data (Swenberg, 1987).

Dose-response models span a hierarchy that reflects an ability to incorporate different kinds of information. If data to support it are available, a mechanism-based procedure is the preferred approach for modeling. A mechanism-based procedure is explicitly devised to reflect biological processes. Theoretical values for parameters, e.g., theoretical cell proliferation rates, are not used to enable application of a mechanism-based model (Portier, 1987). If such data are absent, a mechanism-based model is not used. An example of a mechanism-based model is the receptor mediated toxicity model for dioxin, under development at EPA (U.S. EPA, 1992c).

Dose-response models based on general concepts of a mechanism of action are next in amount of information required. For a specific agent, model parameters are obtained from laboratory studies. Examples are the two-stage models of initiation, clonal expansion, and progression developed by Moolgavkar et al. (1981) and Chen et al. (1991). Such models require extensive data to build the form of the model as well as to estimate how well it conforms with the observed carcinogenicity data.

Empirical models, which do not incorporate information about mechanism of action, form the rest of the hierarchy. Among these, time-to-tumor models incorporate longitudinal information on tumor development. Simple quantal models use only the final incidence at each dose level. The linearized multistage procedure is an example of an empirical model.

If a mechanism-based model is judged to be not suitable, the analysis uses an empirical model whose underlying parameters correspond to the putative mechanism of action identified in the hazard characterization. A multistage

model (Zeise et al., 1987) structured with time to response as the random variable is appropriate when time is the dominant factor for probability of response. This is the approach when available information described in the hazard characterization is consistent with an assumption that there is no threshold of response for individuals. When the probability of effect is due to the distribution of thresholds for individuals in the population, a model considering dose as the random variable may be used. This may be considered an appropriate approach when the mechanism has been identified as one such as disruption of hormone homeostasis.

{The issue of appropriate dose-response models is still under discussion at EPA.}

Ordinarily, models are expected to provide an adequate fit to the observed dose-response information. The outcome of most tests of goodness of fit to the observations is not an effective means of discriminating among models that all provide an adequate fit. Although a model may adequately fit the observed dose-response information, all models have limitations in their ability to describe the underlying processes and make projections outside the observed information. A prime consideration is the potential for model error, that is the possibility that a model might appear to fit the observed data but be based on an inadequate mathematical description of the true underlying mechanism. This is especially crucial when making inferences outside the range of observation, as alternative models may provide an adequate fit to the observed information but have substantially different implications outside the range of observation.

Sometimes an inadequate fit might be improved by incorporating more information. For example, data in which there is high mortality may be poorly fit unless competing risks of death by toxicity are taken into consideration with time-to-tumor information and survival adjustments. If an adequate fit cannot be obtained, it may be necessary to give less weight to the observations most removed from low-dose risk., e.g., from the highest dose level in a study with several dose levels.

Statistical considerations can affect the precision of model estimates. These include the number and spacing of dose levels, sample sizes, and the precision and accuracy of dose measurements. Sensitivity analysis can be performed to describe the sensitivity of the model to slight variations in the observed data. A large divergence between upper and lower confidence bounds indicates that the model cannot make precise projections in that range. All of these considerations are important in determining the range in which a model is supported by data.

With the recent expansion of readily available computing capacity, computer-intensive methods are being adapted to create simulated biological data that are comparable with the observed information. These simulations can be used for sensitivity analysis, for example, to analyze how small, plausible variations

in the observed data could affect the risk estimates. These simulations can also provide information about experimental uncertainty in risk estimates, including a distribution of risk estimates that are compatible with the observed data. Because these simulations are based on the observed data, they cannot, however, assist in evaluating the extent to which the observed data as a whole are idiosyncratic rather than typical of the true state of risks.

The lowest reliable area of a curve is identified as a result of the data modeling. This point is generally at the level of not less than a 1.0 percent response if only animal tumor response data are available. (This 1.0 percent response level is about an order of magnitude below the potential power of a standard rodent study to detect effects.) The lowest reliable area may be extended below a 1.0 percent response if based on a more powerful study, on combined studies, or on joining the analysis of tumor response data with data on other markers of effect. This lowest reliable area provides an estimate that can be used for comparision with similar analyses of the observed range of noncancer effects of an agent (USEPA, 1991f).

3.3.2 Extrapolation

Using the lowest reliable point from the first step of analysis as a point of departure, the preferred approach for this second step of analysis still is a mechanism-based model, if data support it. If a mechanism-based model has been used to portray the observed data, the question in this step is whether confidence in the model extends to using it for extrapolation. If data are insufficient to support a mechanism-based model, extrapolation is done by a default procedure whose parameters reflect the general mechanism or mechanisms of action considered to be supported by the available biological information.

If the mechanism of action being considered leads to an expected linear dose-response relationship, the linearized multistage model or a model-free approach may be appropriate (Gaylor and Kodell, 1980; Krewski, 1984; Flamm and Winbush, 1984).

The mechanism of action being considered may project that the dose-response relationship in the population is most influenced by the differences in sensitivities. In this case, a model including tolerance distribution parameters may be used to provide estimates of the proportion of the population at risk for specific doses of interest, e.g., 1/1000, 1/10000 lifetime risk levels. This approach requires data for a mathematical portrayal of the distribution.

{NOTE: The appropriate empirical modeling approaches for extrapolation are an undecided issue when a putative mechanism of action has been recognized but data are not supportive of a mechanism-based model. Further technical analysis and discussion are necessary before this section can be completed.}

Alternatively, the mechanism may be one that involves a population threshold. In these cases, extrapolation is not made. Instead, a "margin of exposure" presentation is made in the risk characterization. The margin of exposure in this context is the lowest reliable dose-response area from observed data divided by the environmental dose level of interest.

3.3.3 Issues for Analysis of Human Studies

Issues and uncertainties arising in dose-response assessment based on epidemiological studies are analyzed in each case. Several sources of uncertainty need to be addressed in the dose-response analysis. Consideration needs to be given to the data on the exposure and mortality experience of the study population and of the population that will represent the background incidence of the neoplasm(s) involved. In this area, there are potentials for mistakes or uncertainty in the data or adjustments to the data concerning the occurrence or level of exposure of the population members, mortality experience of a population, incomplete follow-up of individuals, exposure (or not) of individuals to confounding causes, or consideration of latency of response. These are assessed by analyzing the sensitivity of dose-response study results to errors where data permit. Other kinds of uncertainty can occur because of small sample size which can magnify the effects of misclassification or change assumptions about statistical distribution that underlie tests of statistical significance (Wyzga, 1988). These uncertainties are discussed. Where possible, analyses of the sensitivity of results to the potential variability in the data in these areas are performed.

The suitability of various available mathematical procedures for quantifying risk attributed to exposure to the study agent is discussed. These methods (e.g., absolute risk, relative risk, excess additive risk) account differently for duration of exposure and background risk, and one or more can be used in the analysis as data permit. The use of several of these methods is encouraged when they can be used appropriately in order to gain perspectives on study results.

3.3.4. Use of Toxicity Equivalence Factors

A toxicity equivalence factor (TEF) procedure is one used to derive quantitative dose-response estimates for agents that are members of a category or class of agents. TEFs are based on shared characteristics that can be used to order the class members by carcinogenic potency when cancer bioassay data are inadequate for this purpose (USEPA, 1991c). The ordering is by reference to the characteristics and potency of a well-studied member or members of the class. Other class members are indexed to the reference agent(s) by one or more shared characteristic to generate their TEFs. The TEFs are usually indexed at increments of a factor of 10. Very good data may permit a smaller increment to be used. Shared characteristics that may be used are, for example, receptor-binding

characteristics, results of assays of biological activity related to carcinogenicity, or structure-activity relationships.

TEFs are generated and used for the limited purpose of assessment of agents or mixtures of agents in environmental media when better data are not available. When better data become available for an agent, its TEF should be replaced or revised.

Guiding criteria for the successful application of TEFs are (USEPA, 1991c):

1. A demonstrated need. A TEF procedure should not be used unless there is a clear need to do so.
2. A well-defined group of chemicals.
3. A broad base of toxicological data.
4. Consistency in relative toxicity across toxicological endpoints.
5. Demonstrated additivity between toxicities of group members for assessment of mixtures.
6. A mechanistic rationale.
7. Consensus among scientists.

3.4. Dose-Response Characterization

The conclusions of dose-response analysis are presented in a characterization section. Because alternative approaches may be plausible and persuasive in selecting dose data, response data, or extrapolation procedures, the characterization presents the judgments made in such selections. The results for the approach or approaches chosen are presented with a rationale for the one(s) that is considered to best represent the available data and best correspond to the view of the mechanism of action developed in the hazard assessment.

The exploration of significant uncertainties in data for dose and response and in extrapolation procedures is part of the characterization. They are described quantitatively if possible through sensitivity analysis and statistical uncertainty analysis. If quantitative analysis is not possible, significant uncertainties are described qualitatively. Dose-response estimates are appropriately presented in ranges or as alternatives when equally persuasive approaches have been found.

Numerical dose-response estimates are presented to one significant figure and qualified as to whether they represent central tendency or plausible upper-bounds on risk or, in general, as to whether the direction of error is to overestimate or under estimate risk. For example, the straight line extrapolation used as a default is typically considered to place a plausible upper- bound on risk at low doses. On the other hand, a tolerance distribution model used as a default to portray risk-specific response distribution of the population may greatly underestimate risks if the mechanism is in fact a linear, nonthreshold one. (Krewski, 1984).

In cases, where a mechanism has been identified that has special implications for early-life exposure, differential effects by sex, or other concerns for sensitive subpopulations, these are explained. Similarly, any expectations that high dose-rate exposures may alter the risk picture for some portion of the population are described. These and other perspectives are recorded to guide exposure assessment and risk characterization.

4. Exposure Assessment

Guidelines for exposure assessment of carcinogenic and other agents are published in USEPA, 1992a. The exposure characterization is a key part of the exposure assessment; it is the summary explanation of the exposure assessment. The exposure characterization

a. provides a statement of purpose, scope, level of detail, and approach used in the assessment;
b. presents the estimates of exposure and dose by pathway and route for individuals, population segments, and populations in a manner appropriate for the intended risk characterization;
c. provides an evaluation of the overall quality of the assessment and the degree of confidence the authors have in the estimates of exposure and dose and the conclusions drawn; and
d. communicates the results of exposure assessment to the risk assessor, who can then use the exposure characterization, along with the characterization of the other risk assessment elements, to develop a risk characterization.

In general, the magnitude, duration, and frequency of exposure provide fundamental information for estimating the concentration of the carcinogen to which the organism is exposed. These data are generated from monitoring information, modeling results, and or reasoned estimates. An appropriate treatment of exposure should consider the potential for exposure via ingestion, inhalation, and dermal penetration from relevant sources of exposures, including multiple avenues of intake from the same source.

Special problems arise when the human exposure situation of concern suggests exposure regimens, e.g., route and dosing schedule that are substantially different from those used in the relevant animal studies. The cumulative dose received over a lifetime, expressed as average daily exposure prorated over a lifetime, is an appropriate measure of exposure to a carcinogen particularly for an agent that acts by damaging DNA. The assumption is made that a high dose of a carcinogen received over a short period of time is equivalent to a corresponding low dose spread over a lifetime. This approach becomes more problematic

as the exposures in question become more intense but less frequent, especially when there is evidence that the agent acts by a mechanism involving dose-rate effects.

5. Characterization Of Human Risk

5.1. Purpose

The risk characterization is prepared for the purpose of communicating results of the risk assessment to the risk manager. Its objective is to be an appraisal of the science that the risk manager can use, along with other decisionmaking resources, to make public health decisions. A complete characterization presents the risk assessment as an integrated picture of the analysis of the hazard, dose response, and exposure. It is the risk analyst's obligation to communicate not only summaries of the evidence and results, but also perspectives on the quality of available data and the degree of confidence to be placed in the risk estimates. These perspectives include explaining the constraints of available data and the state of knowledge about the phenomena studied.

5.2. Application

A risk characterization is a necessary part of any Agency report on risk, whether the report is a preliminary one prepared to support allocation of resources toward further study or a comprehensive one prepared to support regulatory decisions. Even if only parts of a risk assessment (hazard and dose-response analyses for instance) are covered in a document, the risk characterization will carry the characterization to the limits of the document's coverage.

5.3. Content

Each of the following subjects should be covered in the risk characterization.

5.3.1. Presentation and Descriptors

The presentation of the results of the assessment should fulfill the aims as outlined in the purpose section above. The summary draws from the key points of the individual characterizations of hazard, dose response, and exposure analysis performed separately under these guidelines. The summary integrates these characterizations into an overall risk characterization (AIHC, 1989).

The presentation of results clearly explains the descriptors of risk selected to

portray the numerical estimates. For example, when estimates of individual risk are used or population risk (incidence) is estimated, there are several features of such estimates that risk managers need to understand. They include, for instance, whether the numbers represent average exposure circumstances or maximum potential exposure. The size of the population considered to be at risk and the distribution of individuals' risks within the population should be given. When risks to a sensitive subpopulation have been identified and characterized, the explanation covers the special characterization of this population.

5.3.2. Strengths and Weaknesses

The risk characterization summarizes the kinds of data brought together in the analysis and the reasoning upon which the assessment rests. The description conveys the major strengths and weaknesses of the assessment that arise from availability of data and the current limits of understanding of the process of cancer causation. Health risk is a function of the three elements of hazard, dose response, and exposure. Confidence in the results of a risk assessment is, thus, a function of confidence in the results of the analyses of each element. The important issues and interpretations of data are explained, and the risk manager is given a clear picture of consensus or lack of consensus that exists about significant aspects of the assessment. Whenever more than one view of the weight of evidence or dose-response characterization is supported by the data and the policies of these guidelines, and when choosing between them is difficult, the views are presented together. If one has been selected over another, the rationale is given; if not, both are presented as plausible alternative results. If a quantitative uncertainty analysis of data is appropriate, it is presented in the risk characterization; in any case, qualitative discussion of important uncertainties is appropriate.

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Appendix E

Use of Pharmacokinetics to Extrapolate From Animal Data to Humans

Introduction

In classical toxicology, the issue of extrapolation of (usually) animal data to human applications is phrased as:

- Dose to dose (usually high dose in animals to low dose for applications).
- Route to route (e.g., ingestion vs. inhalation).
- Species to species (animal or cell culture to humans).

Pharmacokinetics (PK) can aid in understanding information and in predicting outcomes with respect to the absorption, disposition, metabolism, and excretion of chemicals. Traditionally, analysis has been done empirically, with direct use of the data at hand, and possibly with the aid of simple mathematical models that use overall mass balances. More recently, compartmental models based on chemical transfer in and out of body organs, or even portions of organs, have been developed to describe and predict relationships between administered dose and biologically effective concentrations of parent compounds or metabolites in critical target tissues. These models, which are based on the anatomy and physiology of mammals and use the vast amount of published comparative physiologic data, are known as physiologically based pharmacokinetic (PBPK) models. Details are given in a review by Bischoff (1987).

Each of the three main kinds of extrapolation is briefly described below.

Dose to Dose

PBPK permits reasonable extrapolation from one dose to another, if adequate information on physicochemical properties, physiology, pharmacology, and biochemistry is available. That is not often the case, with less being known as one moves along the list from physiochemical properties to biochemistry; however, PBPK models clearly reveal what data they require and thus what experiments will be needed to make them useful. If the dynamic processes modeled by the PBPK approach are all directly proportional to administered concentrations, then the extrapolation can be relatively straightforward. However, this is not often the case, especially at higher doses, where saturation of metabolic or clearance processes can occur. Despite those difficulties, there are many examples in the literature where useful PBPK analyses have been undertaken. Although PBPK analyses do not always directly address the question of pharmacodynamics (how the biologically effective dose to a critical target tissue is related to toxic response in that tissue), such analyses might provide insight pertinent to this question.

Route to Route

Two broad categories of route-specific toxicity need to be considered: "noncorrosive" and "corrosive." In the former, a chemical enters the body by some route and exerts its effect in the interior of the body; it must enter the blood circulation before it has its effect. In the latter, a very active chemical can have a direct effect at the point of entry, such as high levels of formaldehyde in the case of the rat, nitric acid on skin, or ethylene dibromide at the tip of a gavage tube. Some compounds, such as ethylene dibromide, can be both corrosive and noncorrosive.

Most toxicants are noncorrosive, and knowledge of relevant physiology and pharmacology can permit extrapolation between routes of exposure, because the important information is the concentration in the blood and the transport to and uptake at the site of action. There could still be route-to-route differences, e.g., if the peak concentration after exposure determines toxicity. For example, absorption might be faster (and thus the peak higher) for intravenous than for oral exposure. PBPK models are useful, because they permit estimation of peak concentrations.

Species to Species

Species-to-species extrapolation is one of the most useful aspects of PBPK, because all mammals have the same macrocirculatory anatomy and much is known about the comparative dimensions of their physiologic characteristics—organ volumes, blood flow rates, some clearances, etc. The basic data are usually

presented as a function of body weight raised to some fractional power, W^b, with b = 0.7-1.0 (so-called "allometric scaling"). This aspect is relatively straightforward. However, other aspects can be more complicated, particularly those involving metabolism. For instance, there might be qualitative differences between species, such as the presence or absence of a given enzyme, that would result in a (potentially dose-dependent) difference in metabolic capacity and make their metabolism different.

Appendix F

Uncertainty Analysis of Health Risk Estimates

Introduction

Large uncertainties are typically associated with the estimation of public health risks associated with air toxic emissions. Such uncertainties arise in: (1) the formulation of the models used to simulate the fate and transport of chemicals in the environment and the foodchain, public exposure, dose, and health risks; and (2) the estimation of the parameter values used as input values to these models.

The uncertainty due to model formulation can be reduced to some extent by using models that provide a more comprehensive treatment of the relevant physico-chemical processes. (It should be noted, however, that as a model becomes more comprehensive, the input data requirements may increase substantially; and while the uncertainty associated with the model formulation decreases, the uncertainties associated with the input parameters may increase). Seigneur et al. (1990) provide some guidance on the selection of mathematical models for health risk assessment with various levels of accuracy in their formulation. We focus here on the uncertainties due to the input parameters for a given health risk assessment model.

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Uncertainties in parameter values arise for three reasons. First, the value may have been measured, in which case some imprecision is associated with the process of measurement. In the context of this report, however, errors of measurements are likely to be insignificant compared to other kinds of uncertainty. Second, the value may have been measured, but under circumstances other than those for which it must be applied. In this case, additional uncertainty arises from the variation of the parameter in time and space. Third, the value may not have been measured at all, but estimated from relationships with other quantities that are known or measured. In this case, uncertainty in the parameter of interest arises form both uncertainty in the quantities that are measured and from uncertainty about the estimating relationship.

By characterizing the uncertainties in the input parameters of a model and studying the effects of variation in these parameters on the model predictions, we can estimate the part of the uncertainty in the predictions that is due to uncertainty in the inputs.

Uncertainty can be characterized by a probability distribution. That is, the value of a parameter is not known exactly, but, for example, it might be thought to lie between 90 and 100 with probability 0.5, between 85 and 120 with probability 0.75, and so on. Sometimes such probability distributions can be usefully summarized by a few parameters, such as the mean and standard deviation. Uncertainties in the input parameters propagate through the model to produce probability distributions on the output parameters. Figure 1 presents a schematic description of the uncertainty propagation through a model.

We present here a structured methodology for the parameter uncertainty analysis of health risk estimates. The methodology involves: (1) a sensitivity analysis of the model used to perform the health risk calculations, (2) the determination of probability distributions for a number of selected input parameters (i.e., the ones identified as the most influential to the output variable); and (3) the propagation of the uncertainties through the model.

This methodology is applied here to the uncertainty analysis of the carcinogenic health risks estimated as due to the emissions of a coal-fired plant.

Uncertainty Analysis Methodology

Overview

A health risk assessment model combines a number of models to simulate the transport and fate of chemicals in air, surface water, surface soil, groundwater and the foodchain. Concentrations calculated by the fate and transport models

are used by exposure-dose models to calculate the doses to exposed individuals, which are then used to calculate health risks.

For the description of the uncertainty analysis methodology, we consider each individual model component as a function Y (dependent variable) of a number of parameters X^1, X^2,…X^n (independent variables). In summary, we view this methodology as consisting of the following 5 steps:

Step 1: Sensitivity analysis of the health risk assessment model: This analysis allows one to determine the influential parameters of the model, i.e., those that need to be included in the uncertainty analysis.

Step 2: Parameterization of the health risk assessment by construction of response surface models: This parameterization allows one to simplify the uncertainty propagation and therefore allows the incorporation of a large number of parameters in the analysis.

Step 3: Selection of probability distribution for the input parameters.

Step 4: Propagation of the parameter uncertainties: This task is performed with the parameterized version of the model and provides the uncertainties in the model outputs.

Step 5: Analysis of the probability distribution of the risk estimates.

A more detailed description of each individual step of the methodology is presented in the following paragraphs.

Sensitivity Analysis

Mathematical models describing physical phenomena are often composed of relatively complex sets of equations involving a large number of input parameters. However, some of these parameters do not have any significant influence on the health risk calculated by the model; i.e., the model output is not sensitive to the values of these input parameters. Therefore, such parameters that do not affect the health risk values significantly, do not need to be known with great accuracy and the uncertainty analysis should focus on those parameters to which the calculated health risks are most sensitive.

The sensitivity analysis allows us to determine the parameters to which the model is most sensitive. These parameters will be called the *influential parameters*.

When dealing with a complex model, such as a multimedia health risk assessment model, sensitivity analysis should be performed for each individual model component as well as for the overall model.

The sensitivity of the model output (i.e., the dependent variable) to a model input parameter can be measured by the ratio of the change in the model output to the perturbation in the input parameter. We define this ratio as the sensitivity index, *SI*. For parameter *i*:

$$SI_i = \frac{\Delta Y}{\Delta X_i}$$

where ΔX_i is the perturbation in the input parameter, and ΔY is the corresponding change in the model output. In order to compare the sensitivity index for various input parameters, it is appropriate to use a dimensionless representation of the sensitivity index:

$$SI_i^* = \frac{\Delta Y / \bar{Y}}{\Delta X_i / \bar{X}_i} = \frac{\Delta Y^*}{\Delta X_i^*}$$

where $\bar{X}_i$ and $\bar{Y}$ are the mean or some other reference values of the variables, X_i and Y, respectively; and ΔY^* and ΔX_i^* refer to normalized perturbations.

Two characteristics of the sensitivity index must be noted:

- The value of the sensitivity index is a function of the value of and the perturbation in the input parameter except for cases where the relationship between the model output variable and the input parameter is linear.
- The value of the sensitivity index may be a function of the value of the other model input parameters except for cases where the relationship between the model output and the input parameters is linear.

Even though the sensitivity index, as defined above, sufficiently describes the effect on the model result for a given change in the input parameter, it does not provide a measure of the range of variation in the model output, given the expected range of variation of the input parameter. In other words, a parameter that has a high sensitivity index, may have little effect on the model output if that parameter can only have a very small variation. The height of a power plant stack is an example of a parameter that has significant effect on atmospheric ground-level concentrations but has a small uncertainty. For the case of the power plant studied here, a 100% change in stack height caused a 73% change in the resulting concentrations. Since the uncertainty in stack height, however, can only be due to measurement error, it is not expected to be more than ±2%. Consequently, the actual influence of this parameter on the model result is very small.

We define the uncertainty index as a measure of uncertainty associated with a parameter X_i. Although several definitions of this uncertainty index are possible,

we select one that is objective in a statistical sense by using the standard deviation and the mean of the parameter. The uncertainty index is defined as follows:

$$UI_i = \frac{\sigma_i}{\bar{X}_i}$$

where: σ_i is the standard deviation of the parameter distribution $\bar{X}$ is the mean value of parameter X_i

The uncertainty index, consequently provides a measure of the expected variation of parameter X_i over its range of probable values.

The combination of the model sensitivity to a parameter, and the uncertainty in that parameter provides the information required to assess which parameters need to be included in the uncertainty analysis. We define a sensitivity/ uncertainty index as follows:

$$I_j = (SI_i)(UI_i) = \frac{\Delta Y^*}{\Delta X_i^*}\frac{\sigma_i}{\bar{X}_i}$$

The sensitivity/uncertainty index, therefore constitutes a representative measure of the influence that a parameter has on the model results and can, thus, be used to select the model influential parameters to be included in the uncertainty analysis. Figure 2 presents a schematic description of the steps followed in the sensitivity analysis procedure.

Even though the concept of the standard deviation of a parameter was used in the definitions of the uncertainty and sensitivity/uncertainty indexes, it is rather unlikely that actual standard deviations will be available for all the parameters examined in the sensitivity analysis. Since the sensitivity analysis is a screening procedure whose goal is to minimize the number of parameters included in the final uncertainty analysis, it is generally appropriate to use other measures that are more readily available to characterize the variability of a parameter. For example, the expected range of variation can be used instead of an actual standard deviation.

Parameterization of the Mode—Response Surface Construction

A multimedia health risk assessment model typically involves a large number of input parameters and comprises several individual models for simulating fate and transport, exposure, dose, and health effects. Such a model can be computationally very demanding and performing an uncertainty analysis for a large number of parameters may, therefore, not be feasible. It is, therefore, necessary to parameterize the various model components in order to reduce the magnitude of

the computations. This model parameterization can be achieved by constructing response surfaces.

A response surface is a simplified version of the actual model which can be used efficiently in the uncertainty analysis as a replacement of the real model. In the case of simple analytical models in the form of a single equation (e.g., dose models) only minor simplifications need to be made for the construction of the response surface. Such simplifications can be accomplished by factoring out of each of the terms of the equation the selected influential parameters, and representing the remaining part of the term by a lumped parameter calculated from previous results of the model. So, the response surface can be of the following form:

$$rY = \sum_{i=1}^{m} \left(X_{i1}^{P_{i1}} \ldots X_{1K_i}^{P_{1K_i}} \right) A_i$$

where: m = Number of terms in dependent variable expression

K_i = Number of independent variables included in term i

A_i = Calculated lumped parameter of term i

In the case of complex models (e.g., environmental transport models) the response surface can be developed using the following procedure: For all influential parameters of a model component select a number K of parameter sets $X_i = (X_{i1} \ldots X_{ln})$ $i = 1, K$ and perform experimental runs of the actual complex model. Then use the pairs of parameter sets $X_1 \ldots X_k$ and corresponding model results $Y_1 \ldots Y_k$ to construct the response surface.

A simple example of a response surface can be that of the atmospheric transport model, in which the air concentration, C_a can be expressed in terms of four independent influential parameters and six constant parameters as follows:

$$\begin{aligned} & C_a = Q_e F_1 F_2 \\ \text{where:} \quad & F_1 = A_1 + A_2 V_s = A_3 V_3^2 \\ & F_2 = A_4 + A_5 (T_s - T_a) + A_6 (T_s - T_a)^2 \end{aligned}$$

where: C_a = Chemical concentration in air

Q_e = Chemical emission rate

V_s = Stack exit velocity

T_s = Stack exit temperature

T_a = Ambient air temperature

A_i = Calculated constant parameters (functions of meteorological data, source characteristics and environmental setting)

A response surface is a parameterization of the model that allows one to calculate the model results with considerably less computations. However, a response

surface is typically specific to a given model application. That is, some of the case study characteristics (e.g., meteorology, hydrology) are implicitly included in the constant parameters of the response surfaces.

Selection of the Probability Distributions for the Input Parameters

Once the influential parameters have been identified, and the response surfaces for each model component constructed, probability distributions must be selected to represent each one of the parameters.

As was mentioned previously, a parameter value can be either directly measured or indirectly estimated through an estimation procedure which usually involves fitting of a curve through a set of experimental points.

In the case of a directly measured parameter, the uncertainty results from uncertainty in the measurement process, and this can sometimes be estimated from repeated measurements. Often, however, the amount of available data is not enough to produce meaningful histograms or probability plots. What is usually available is a range of values within which the true value of a parameter is expected to lie, and possibly a most likely, or range of most likely values for the parameter. In this case, it is left to our judgment and experience to decide what probability distribution is appropriate.

In the case of parameters estimated indirectly through curve fitting (e.g., bioconcentration factors, and cancer potency factors) uncertainty results from both statistical errors in fitting the curve, which can be estimated by statistical procedures, and uncertainty about the form of the curve, which is a matter of judgment.

The development of parameter probability distributions through a combination of *a priori* expert judgment along with current information in the form of available direct or indirect measurements is known in statistical theory as the Bayesian method. If the measurements are direct, precise, and numerous enough to sufficiently describe the variation pattern of the parameters, then the *a priori* judgment may have little or no influence on the resulting probability distributions. Conversely, if the measurements are indirect and imprecise, then the *a priori* judgment may be of great importance.

Propagation of the Model Uncertainties

At this step, the response surfaces developed for the different model components can be combined in a single spreadsheet that performs the function of the overall risk assessment model in a simplified fashion for the case study considered. Several techniques exist to develop a probability distribution in the model output

given probability distributions in the model input parameters. Monte-Carlo and Latin hypercube simulations are standard examples of such techniques. In the special cases where the probability distributions are similar and simple (e.g., normal), the probability distribution in the model output can be calculated analytically. For the general case where no simple analytical approach can be used, however, the spreadsheet model can then be coupled to one of several commercial software packages (e.g., @Risk; Palisade Corp., 1991), which uses the specified probability distributions of the parameters together with the spreadsheet calculations to generate a set of synthetic model results.

Analysis of the Probability Distribution of the Model Health Risk Estimates

If the number of replications for the probabilistic synthetic simulations is large enough, the synthetic results can be statistically analyzed to yield a reasonably reliable probability distribution of the dependent variable (i.e., health risk). If the uncertainty analysis procedure was performed correctly, this probability distribution should represent a more complete and realistic characterization of the anticipated health risks, as it provides a range of possible values accompanied by their corresponding likelihoods instead of a single, deterministic point estimate.

Description Of The Multimedia Health Risk Assessment Model

In this section, we present a description of the multimedia health risk assessment model which was used in the application. This model was developed by combining a number of individual models that handle the fate and transport of chemicals in air, surface water, surface soil, groundwater, and the foodchain, into an integrated multimedia model. A brief description of its individual components, and its overall structure are provided in the following paragraphs. A detailed description is provided by Constantinou and Seigneur (1992).

The model consists of the following nine distinct components:

- Atmospheric fate and transport model
- Deposition model
- Overland model
- Surface water fate and transport model
- Vadose zone fate and transport model
- Groundwater fate and transport model
- Foodchain fate and transport model
- Exposure and dose model
- Health risk model

The multimedia health risk assessment model combines all the model components into a single computer program that takes as input emission stream characteristics and environmental physical parameters, and calculates the resulting carcinogenic and noncarcinogenic health effects. Figure 3 represents the general calculation steps that lead to the final model results.

Deterministic Health Risk Assessment

The boiler of the power plant studied in this application is a 680 MW unit which burns high-sulfur bituminous coal. Four chemicals with listed carcinogenic effect were sampled from the 200m high stack of the facility. Stack air emissions were the only emissions considered in the analysis. Liquid and solid waste discharges were ignored.

The study area examined in the present application was defined to be the area within a 50 km radius of the power plant. This area was divided into 40 subregions by a concentric grid. The major surface water bodies included in the area include a river and a large lake. For the health effect calculations, all public water supply was considered to come from the river and all fish supply was considered to come from the lake.

Carcinogenic and noncarcinogenic health effects were calculated in each of the subregions considered in the study area. The results subject to the uncertainty analysis presented in this report correspond to the carcinogenic health effects in the subregion of maximum risk. Noncarcinogenic risks are not addressed here.

The carcinogenic chemicals detected in the stack air emissions were chromium, arsenic, cadmium, and benzene. The corresponding chemical emission rates were estimated to be 1.08×10^{-2}, 4.4×10^{-4}, 5.39×10^{-4}, and 1.4×10^{-2} g/s, respectively. Since chemical speciation for chromium was not available, the corresponding health effect calculations were performed based on the assumption that total chromium emissions consisted of 5% Cr(VI) and 95% Cr(III). The cumulative carcinogenic lifetime risk from all chemicals and pathways in the subregion of maximum risk was calculated to be 2.2×10^{-8}.

Chromium (VI) and arsenic were calculated to be the two major contributors to carcinogenic risk with contributions of 59 and 32%, respectively. Cadmium contributed 8%, and the contribution of benzene was 1%. Among the three exposure pathways considered in the analysis, inhalation was calculated to be the major contributor, with a contribution of 85%. Ingestion ranked second with 15%, and dermal absorption had an insignificant contribution of 0.4%.

Produce was calculated to be the foodchain component which contributed the

most to the ingestion risk, with a contribution of 92%. Fish and soil ingestion had small contributions of 5 and 3%, respectively, and drinking water had an insignificant contribution of 0.3%.

It should be noted that among the four carcinogenic chemicals included in the analysis, only arsenic and benzene are considered to be carcinogenic through noninhalation pathways. Since benzene's contribution was very small, benzene was not included in the uncertainty analysis. Even though arsenic is considered carcinogenic through the ingestion pathway, no cancer potency value is currently tabulated (October, 1992) for this pathway in the Integrated Risk Information System (IRIS) database. The value used for this parameter in the deterministic health risk assessment was the most recent value listed in IRIS.

Uncertainty Analysis

Sensitivity Analysis

Sensitivity analysis of the individual model components as well as the overall multimedia health risk assessment model was performed to help identify the influential parameters. A total of 49 parameters were examined, and 22 were selected to be included in the final uncertainty analysis, based on their calculated sensitivity/uncertainty indexes. Table 1 provides a list of all parameters examined, together with their corresponding symbols and units.

Sensitivity/uncertainty indexes of the input parameters were derived for each of the individual model components as well as for the overall risk assessment model. The resulting indexes for the three chemicals included in this analysis are summarized in Table 2.

Model Simplification

Using the influential parameters selected, response surfaces were constructed for each of the multimedia health risk assessment model components. In the case of simple models such as the foodchain, exposure-dose, and risk models, the response surfaces were constructed manually by factoring out the influential parameters, and representing the remaining parts of the equations by constants calculated based on the model results. In the case of the more complex environmental transport models, additional sensitivity runs were performed by varying the influential parameters within their assumed range of variation.

In the case of the atmospheric transport model, ISC-LT, four influential parameters were identified: the chemical emission rate (Q_e), the stack exit velocity (V_s), the stack exit temperature (T_s), and the ambient air temperature (T_a). The influences

of T_s and T_a were found to be correlated, as what affected the results was the difference between the stack and the ambient temperature, (T_s - T_a) and not their absolute values. Consequently, the two parameters were treated together as one, the temperature difference (T_s - T_a).

Multiple runs were performed by varying V_s and (T_s - T_a) within their assumed range of variation to identify their individual and combined effect on the resulting maximum ground level chemical concentration. Both parameters were found to affect the model results in an exponentially decaying way (i.e., resulting concentrations decreased exponentially for higher values of V_s and (T_s - T_a)) and their variation patterns were fit at the reference point (i.e., parameter values used in the deterministic calculations) by second degree polynomials.

The combined response surface for both parameters was derived by combining their individual curves. It should be noted that this approach is only valid for the range of perturbations considered in this analysis. For larger ranges of parameter variation the model response surface for two or more influential parameters should be derived through multiple regression, where the variation of the model results is examined simultaneously for all parameters. Figure 4 provides a graphical presentation of the derived ISC-LT response surface.

The complete set of equations of the simplified multimedia health risk assessment model is presented below:

- Atmospheric Transport Model (Component 1):

$$C_a = \alpha Q_e F_1 F_2 A_{11}$$

where:

$$F_1 = A_{12} + A_{13} V_s + A_{14} V_s^2$$

$$F_2 = A_{15} + A_{16}(T_s - T_a) + A_{17}(T_s - T_a)^2$$

where: C_a = Ground-level air concentration; Q_e = Chemical emission rate; α = Chemical speciation fraction (applies only to chromium case); V_s = Stack exit velocity; T_s = Stack exit temperature; T_a = Ambient temperature; A_{1j} = Constant j for model component 1

- Deposition Model (Model Component 2):

$$DR = C_a(V_d + V_w A_{21}) A_{22}$$

where: DR = Chemical deposition rate; V_d = Dry deposition velocity; V_w = Wet deposition velocity; A_{2j} = Constant j for model component 2

- Overland Model (Model Component 3):

$$L_{ss} = DR(1-OR_f)A_{3j}$$

where: L_{ss} = Surface soil chemical load; OR_f = Fraction of deposited chemical attributed to overland runoff; A_{3j} = Constant j for model component 3

- Soil Transport Model (Model Component 4)

$$C_s = L_{ss}d_s^{-1}(EST + ED/2)p_b^{-1}A_{4j}$$

where: C_s = Surface soil concentration; d_s = Surface soil depth; EST = Exposure starting time; ED = Exposure duration; p_b = Soil bulk density; A_{4j} = Constant j for model component 4

- Foodchain Model—Plants (Model Component 5):

$$C_p = C_s BCF_p$$

where: BCF_p = Soil-to-plant bioconcentration factor

- Dose Model (Model Component 6):

(1) Inhalation

$$D_1 = C_s IR\ ED\ BW^{-1}A_{6j}$$

where: D_1 = Inhalation dose; IR = Inhalation rate; B_W = Body Weight; A_{6j} = Constant j for model component 6

(2) Ingestion

$$D_2 = (C_p INR_p + A_{62})ED\ BW^{-1}A_{63}$$

where: D_2 = Ingestion dose; INR_p = Plant ingestion rate

- Risk Model (Model Component 7)

$$R = D_1 CPF_1 + D_2 CPF_2 + A_{7j}$$

where: R = Total Carcinogenic risk; CPF_1 = Inhalation cancer potency factor; CPF_2 = Ingestion cancer potency factor; A_{7j} = Constant j for model component 7

It should be noted that the full set of equations presented above applies only to the arsenic case. Cadmium and chromium are not considered carcinogenic through noninhalation pathways. Consequently, only the atmospheric transport, inhalation dose, and inhalation risk equations apply to their case.

Probability Distribution Selection

Evaluation of the probability distributions of the 22 influential parameters of the model was performed on the basis of available statistical data, literature value ranges, and personal judgment. The selected probability distributions, and the information which the distribution types and parameters where based on are summarized in Table 3.

In a health risk assessment, the uncertainty associated with the health effect parameters (i.e., cancer potency factors in the case of the present application) is of major importance. The EPA recommended values for these parameters are usually derived based on limited animal or epidemiological studies the conditions of which may differ significantly from the conditions for which these values will be applied in a risk assessment.

In the case of epidemiological studies, uncertainty is associated with high-to-low dose extrapolation and factors related to secondary exposures, diet, and hygiene of the population under study. The data are fitted by an assumed model, and the maximum lifetime estimate (MLE) is usually recommended for use by EPA.

In the case of animal studies, uncertainty is associated with interspecies as well as high-to-low dose extrapolations. Due to the additional uncertainty of interspecies extrapolation in this case an upper bound value (95^{th} percentile) is usually recommended for use by EPA.

The cancer potency factors for the three chemicals included in this application were all derived based on epidemiological studies.

In the case of arsenic inhalation, the CPF derivation was based on two separate U.S. smelter worker populations (EPA, 1984a). The data collected were analyzed by five different investigators who derived five different CPF values, using a linear nonthreshold model. The EPA recommended value was derived by obtaining the geometric mean of the individually derived CPFs. In this application we chose to represent the uncertainty of the arsenic inhalation CPF by a uniform distribution extending over the range of values provided by the above mentioned five investigators.

In the case of arsenic ingestion, the CPF derivation was based on an epidemiological study of a Taiwanese population exposed to high arsenic concentrations in drinking water (EPA, 1984a). Analysis of these data resulted in a CPF which was later deemed overconservative by EPA, after comparison with the results of limited U.S. studies. Its high value was attributed to underestimation of the exposure of the Taiwanese population, and the lack of consideration of the population's

poor diet and hygiene in the analysis. The value was then scaled by EPA to a lower value that would be more representative for a U.S. population. Due to the uncertainties associated with its derivation, this CPF was recently removed from IRIS until a more reliable value could be derived. In this application we chose to represent the uncertainty of the arsenic ingestion CPF by a triangular distribution with lower bound equal to zero, most likely value equal to the scaled value most recently listed in IRIS (September, 1991), and upper bound equal to the value originally derived from the Taiwanese population data.

In the case of cadmium inhalation, the CPF derivation was based on epidemiological data of a U.S. smelter worker population (EPA, 1985). The EPA-recommended value was determined by fitting a linear nonthreshold model to these data. A 90% confidence interval based only on statistical consideration was constructed around the MLE. In this application we chose to represent uncertainty associated with the cadmium inhalation CPF by a normal probability distribution with mean equal to the maximum likelihood estimate and standard deviation calculated from the estimated confidence interval.

In the case of chromium (VI) inhalation, the CPF was based on a U.S. population of chromate plant workers (EPA, 1984b). The EPA-recommended value was derived by fitting a two-stage model to the data. A lower bound and an upper bound were constructed around the MLE to account for the possibility of underestimation or overestimation of the exposure due to lack of consideration of poor hygiene, smoking habits, and chemical speciation in the analysis. In this application, we chose to represent the uncertainty associated with the chromium (VI) CPF by a triangular distribution defined by the best estimate, upper, and lower bounds.

Monte Carlo Analysis—Health Risk Probability Distribution

The derived response surfaces were combined in a simplified spreadsheet model which was coupled to the software package @RISK (Palisade Corporation, 1991) which performed the propagation of the input parameter uncertainties through the model. A Monte Carlo analysis with 5000 iterations of the simplified model was performed to produce a synthetic set of carcinogenic health risks associated with the studied coal-fired power plant. Statistical analysis of the synthetic results yielded a probability distribution for the risk. The risk value calculated in the deterministic risk assessment (2.2×10^{-8}) was estimated to be at the 83rd percentile of the derived probability distribution. The statistical parameters of this distribution are summarized below:

- Mean (expected value), $\mu = 1.5 \times 10^{-8}$ (i.e., 68% of the deterministic value)

- Mode (most probable value), $M_o = 2.5 \times 10^{-9}$
- Standard Deviation, $\sigma = 3.4 \times 10^{-8}$
- Skewness, $\gamma = 13.6$ (i.e., positively skewed-right tail)
- Percentiles: 5%, $F_{0.05} = 1.2 \times 10^{-9}$; 25%, $F_{0.25} = 3.2 \times 10^{-9}$ Median 50%, $F_{0.5} = 6.9 \times 10^{-9}$; 75%, $F_{0.75} = 1.6 \times 10^{-9}$; 95%, $F_{0.95} = 5.1 \times 10^{-9}$

The derived probability density plot is presented in Figure 5.

Conclusion

A general methodology for the performance of sensitivity/uncertainty analysis was presented. The methodology was applied to a multimedia health risk assessment model. A case study of a coal-fired power plant was used as the basis of this application. The uncertainty of the carcinogenic risk associated with the power plant emissions was examined. The results indicated that the deterministic risk value calculated in the original risk assessment study was a conservative estimate, corresponding to a higher risk percentile on the estimated risk probability distribution.

Acknowledgments

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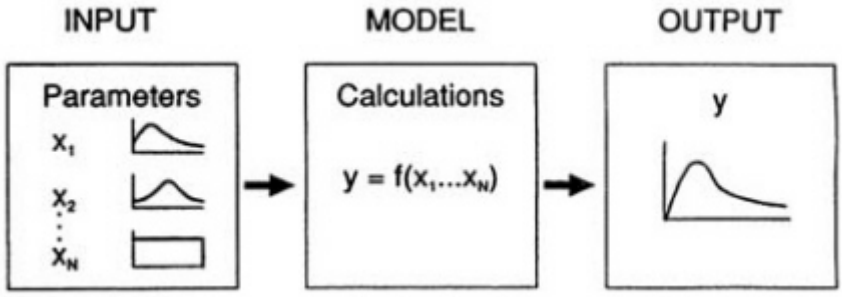

FIGURE 1 Uncertainty Propagation

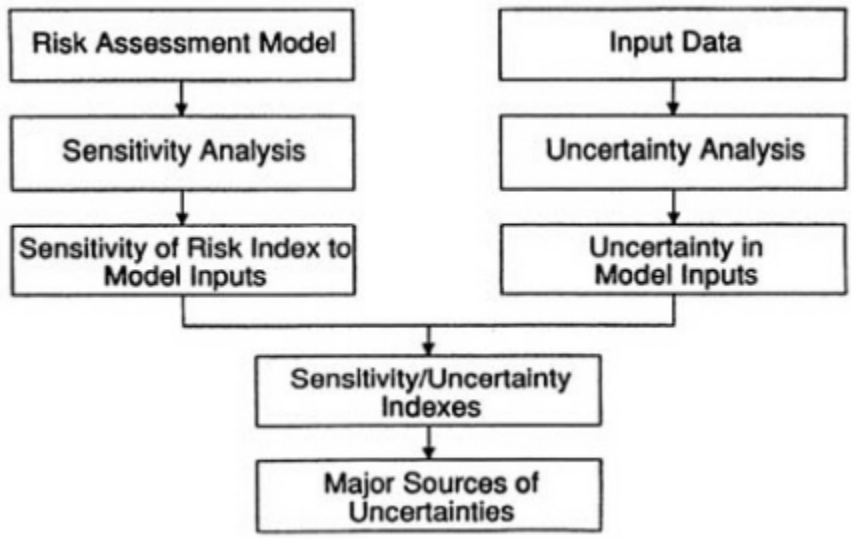

FIGURE 2 Sensitivity Analysis Summary

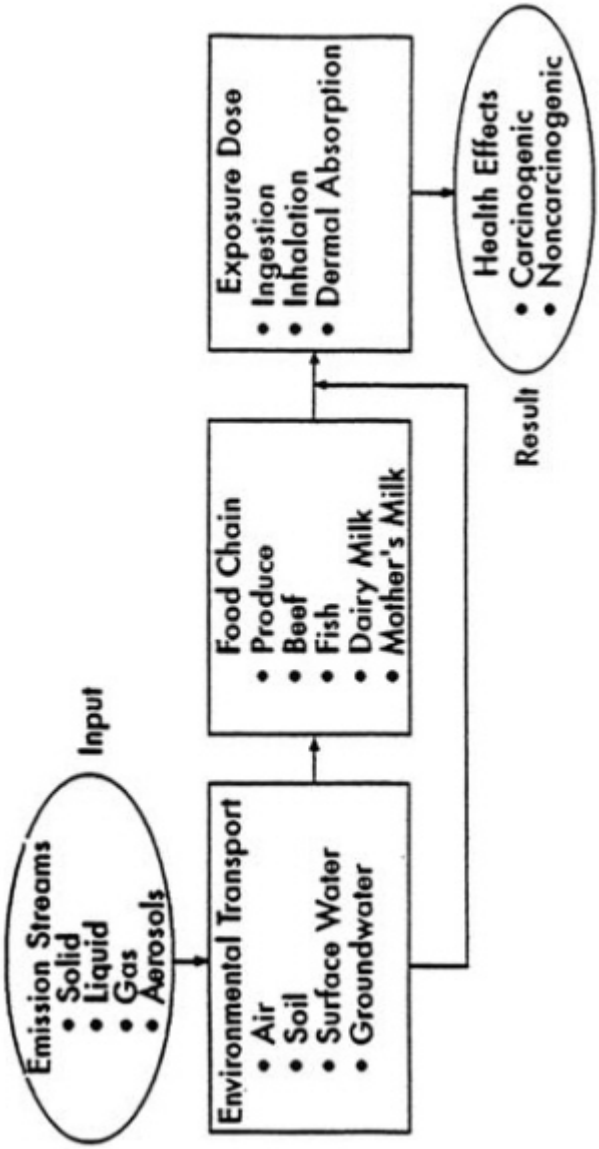

FIGURE 3 Multimedia Health Risk Assessment Model

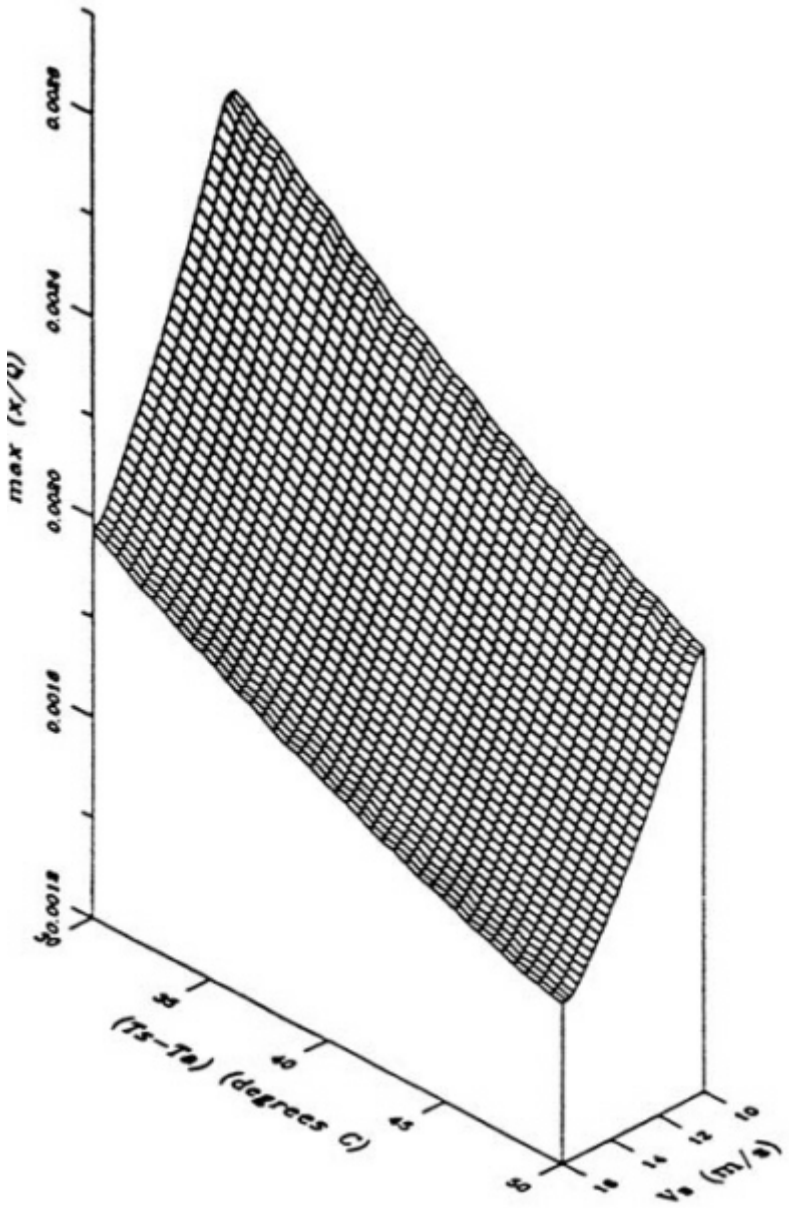

FIGURE 4 ISC-LT Response Surface

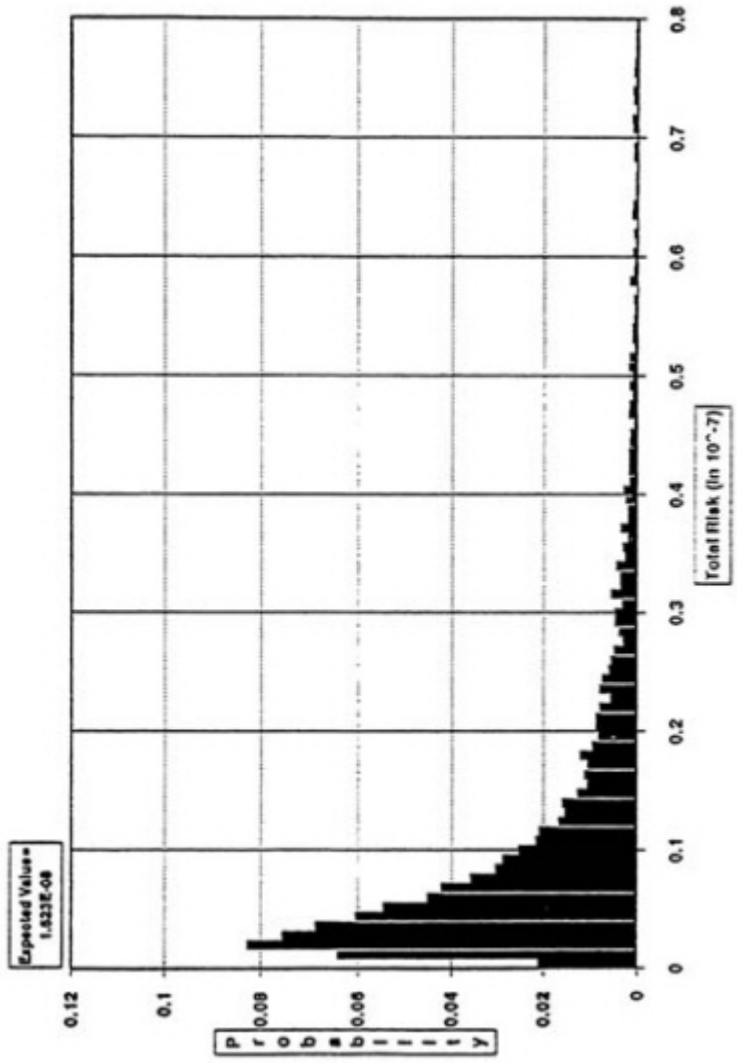

FIGURE 5 Total Carcinogenic Risk Probability Distribution

TABLE 1 Parameter Reference List

Parameter Index	Parameter Description	Parameter Symbol (Units)
1	Chemical Emission Rate - Arsenic	Q_{e1} (g/s)
2	Chemical Emission Rate - Cadmium	Q_{e2} (g/s)
3	Chemical Emission Rate - Chromium	Q_{e3} (g/s)
4	Chemical Speciation Fraction	$\alpha_{(-)}$
5	Stack Height	H_s (m)
6	Stack Exit Temperature	T_s (K)
7	Stack Exit Velocity	V_s (m/s)
8	Stack Diameter	D_s (m)
9	Ambient Temperature	T_a (K)
10	Mixing Height	h_m (m)
11	Arsenic Dry Deposition Velocity	$V\sigma$ (m/s)
12	Wet Deposition Velocity	V_w (m/s)
13	Fraction of Time with Rain	R_f (-)
14	Fraction of Chemical in Overland Runoff	OR_f (-)
15	River Discharge	Q_r (m^3/s)
16	Arsenic Chemical Decay Coefficient in River	K_r (d^{-1})
17	Lake Water Exchange Rate	Q_L (m^3/s)
18	Arsenic Chemical Decay Coefficient in Lake	K_L (d^{-1})
19	Surface Soil Depth	d_s (m)
20	Exposure Duration	ED (years)
21	Exposure Starting Time	EST (years)
22	Cation Exchange Capacity	CEC (meq/100cc)
23	Arsenic Chemical Decay Coefficient in Soil	KDES (d^{-1})
24	Soil Permeability	kp (cm^2)
25	Soil Porosity	θ
26	Soil Bulk Density	ρ_b (kg/m^3)
27	Chemical Plant Interception Fraction	IF (-)

Parameter Index	Parameter Description	Parameter Symbol (Units)
28	Weathering Elimination Rate	K_{et} (d^{-1})
29	Crop Density	CD (kg/m^2)
30	Arsenic Soil-to-Plant Bioconcentration Factor	BCF_p (-)
31	Arsenic Water-to-Fish Bioconcentration Factor	BCF_f (-)
32	Inhalation Rate	IR (m^3/d)
33	Plant Ingestion Rate	INR_p (kg/d)
34	Soil Ingestion Rate	INR_s (kg/d)
35	Water Ingestion Rate	INR_w (I/d)
36	Fish Ingestion Rate	INR_f (kg/d)
37	Skin Surface Area Exposed to Soil	SA_s (cm^2)
38	Soil Absorption Factor	ABS (-)
39	Soil Adhesion Factor	AF (mg/cm^2)
40	Soil Exposure Frequency	EF_s (d/yr)
41	Skin Surface Area Exposed to Water	SA_w (cm^2)
42	Arsenic Permeability Constant	PC (cm/hr)
43	Water Exposure Frequency	EF_w (d/yr)
44	Body Weight	BW (kg)
45	Inhalation Cancer Potency Factor - Arsenic	CPF_{11} (kg-d/mg)
46	Ingestion Cancer Potency Factor - Arsenic	CPF_{21} (kg-d/mg)
47	Dermal Absorption Cancer Potency Factor - Arsenic	CPF_{31} (kg-d/mg)
48	Inhalation Cancer Potency Factor - Cadmium	CPF_{12} (kg-d/mg)
49	Inhalation Cancer Potentcy Factor - Chromium (VI)	CPF_{13} (kg-d/mg)

TABLE 2 Sensitivity/Uncertainty Indexes

Model component	Output variable description	Output variable symbol	Parameter Symbol	Model Component Sensitivity/Uncertainty Indexes			Overall Model Sensitivity/Uncertainty Indexes		
				Chromium (VI)	Arsenic	Cadmium	Chromium (VI)	Arsenic	Cadmium
ISCLT	Air Concentration	C_a	$Q_{e\,(1,2,3)}$	0.91	0.38	1.19	0.91	0.38	1.19
α	0.60	NA	NA	0.60	NA	NA			
H_s	-0.03	-0.03	-0.03	-0.03	-0.03	-0.03			
T_s	-0.07	-0.07	-0.07	-0.07	-0.07	-0.07			
V_s	-0.14	-0.14	-0.14	-0.14	-0.14	-0.14			
D_s	-0.03	-.003	-0.03	-0.03	-0.03	-0.03			
T_a	0.07	0.07	0.07	0.07	0.07	0.07			
h_m	0.02	0.02	0.02	0.02	0.02	0.02			
Deposition	Deposition Rate	DR	V_d	NA	0.76	NA	NA	0.35	NA
			V_w	NA	0.24	NA	NA	0.11	NA
			R_f	NA	0.05	NA	NA	0.02	NA
Overland	Surface Soll Load	L_{ss}	OR_f	NA	-0.18	NA	NA	-0.07	NA
WTRISK	Surface Water Concentration	C_{sw}	Q_r	NA	-0.09	NA	NA	-0.002	NA

Model Component	Ouput Variable Description	Output Variable Symbol	Parameter Symbol	Model Component Sensitivity/Uncertainty Indexes			Overall Model Sensitivity/Uncertainty Indexes		
				Chromium (VI)	Arsenic	Cadmium	Chromium (VI)	Arsenic	Cadmium
WTRISK	Surface Water Concentration		K_r	NA	0.0	NA	NA	0.0	NA
			Q_L	NA	-0.09	NA	NA	-0.002	NA
			K_L	NA	0.0	NA	NA	0.0	NA
SESOIL	Surface Soil Concentration	C_{ss}	d_s	NA	-0.67	NA	NA	-0.29	NA
ED	NA	0.20	NA	NA	0.09	NA			
EST	NA	1.43	NA	NA	0.64	NA			
CEC	NA	0.0	NA	NA	0.00	NA			
KDES	NA	0.0	NA	NA	0.00	NA			
k_p	NA	0.0	NA	NA	0.00	NA			
θ	NA	0.0	NA	NA	0.00	NA			
ρb	NA	-0.18	NA	NA	-0.08	NA			
AT123D	NA	NA	NA	NA	NA	NA	NA	NA	NA
Food Chain	Plant Concentration	C_v	IF	NA	0.00	NA	NA	0.00	NA

Model Component	Output Variable Description	Output Variable Symbol	Parameter Symbol	Model Component Sensitivity/Uncertainty Indexes			Overall Model Sensitivity/Uncertainty Indexes		
				Chromium (VI)	Arsenic	Cadmium	Chromium (VI)	Arsenic	Cadmium
Food Chain	Plant Concentration		K_{el}	NA	0.00	NA	NA	0.00	NA
			CD	NA	0.00	NA	NA	0.00	NA
			BCF_p	NA	0.5	NA	NA	0.21	NA
	Fish Concentration	C_f	BCF_f	NA	0.5	NA	NA	0.01	NA
Dose	Inhalation Dose	D_1	IR	0.40	0.40	0.40	0.21	0.21	0.21
Ingestion	D_2	INR_p	NA	1.32	NA	NA	0.60	NA	
Dose		INR_s	NA	0.05	NA	NA	0.02	NA	
		INR_w	NA	0.00	NA	NA	0.00	NA	
		INR_f	NA	0.02	NA	NA	0.01	NA	
Dermal	D_3	SA_s	NA	0.40	NA	NA	0.005	NA	
Absorption		ABS	NA	0.50	NA	NA	0.007	NA	
Dose		AF	NA	0.50	NA	NA	0.007	NA	

Model Component	Output Variable Description	Output Variable Symbol	Parameter Symbol	Model Component Sensitivity/Uncertainty Indexes			Overall Model Sensitivity/Uncertainty Indexes		
				Chromium (VI)	Arsenic	Cadmium	Chromium (VI)	Arsenic	Cadmium
Dose	Dermal		EF_s	NA	0.50	NA	NA	0.007	NA
	Absorption		SA_w	NA	0.00	NA	NA	0.00	NA
	Dose		PC	NA	0.00	NA	NA	0.00	NA
			EF_w	NA	0.00	NA	NA	0.00	NA
	All Doses	D_1, D_2, D_3	BW	-0.28	-0.28	-0.28	-0.28	-0.28	-0.28
Risk	Total	R	$CPF_{1(1, 2, 3)}$	3.39	0.39	0.93	3.39	0.39	0.93
	Carcinogenic		$CPF_{2(1, 2, 3)}$	NA	1.91	NA	NA	1.91	NA
	Risk		$CPF_{3(1, 2, 3)}$	NA	0.01	NA	NA	0.01	NA

Note: The above listed Overall Model Sensitivity/Uncertainty Indexes correspond to the carcinogenic risk of each individual chemical.

TABLE 3 Probability Distribution Selection

Influential Parameter index	Parameter Symbol	Probability Distribution	
		Type	Parameters
1	Q_{e1} - Arsenic	Lognormal	$\mu'_{} = -7.76$, $\sigma'_{} = 0.39$
2	Q_{e2} - Cadmium	Lognormal	$\mu'_{} = -7.73$, $\sigma'_{} = 1.06$
3	Q_{e3} - Chromium	Lognormal	$\mu'_{} = -5.25$, $\sigma'_{} = 1.30$
4	$_{a}$-Chrom (VI)	Normal	$\mu_{} = 0.06$, $\sigma_{} = 0.015$
5	T_s	Uniform	$_{a} = 318$, $_{b} = 328$
6	V_s	Uniform	$_{a} = 10.4$, $_{b} = 15.6$
7	T_a	Uniform	$_{a} = 278$, $_{b} = 288$
8	V_d	Normal	$\mu_{} = 0.005$, $\sigma_{} = 0.0025$
9	V_w	Normal	$\mu_{} = 0.1$, $\sigma_{} = 0.05$
10	OR_f	Normal	$\mu_{} = 0.47$, $\sigma_{} = 0.047$
11	d_s	Lognormal	$\mu'_{} = -3.10$, $\sigma'_{} = 0.75$
12	ED	Lognormal	$\mu'_{} = 2.24$, $\sigma'_{} = 0.58$
13	EST	Uniform	$_{a} = 0$, $_{b} = 100$
14	p_b	Normal	$\mu_{} = 1550$, $\sigma_{} = 175$
15	BCF_p	Uniform	$_{a} = 0.01$, $_{b} = 0.05$
16	IR	Triangular	$_{a} = 14$, $_{m} = 22$, $_{b} = 30$
17	INR_p	Lognormal	$\mu'_{} = -2.58$, $\sigma'_{} = 0.61$
18	BW	Normal	$\mu_{} = 71.5$, $\sigma_{} = 17.0$
19	CPF_{11} - Arsenic	Uniform	$_{a} = 4.4$, $_{b} = 26.7$
20	CPF_{21} - Arsenic	Triangular	$_{a} = 0$, $_{m} = 1.75$, $_{b} = 15.0$
21	CPF_{12} - Cadmium	Normal	$\mu_{} = 6.3$, $\sigma_{} = 2.93$
22	CPF_{13} - Chromium	Triangular	$_{a} = 10.5$, $_{m} = 42.1$, $_{b} = 295.2$

Explanations: The above-listed probability distribution types are defined as follows:

- Uniform where: $_{[a.\ b]}$ $_{a}$ = minimum value, $_{b}$ = maximum value
- Normal where: (μ, σ) μ = distribution mean, σ = distribution standard deviation
- Triangular where: $_{[a.\ m.\ b]}$ $_{a}$ = minimum value, $_{m}$ = most likely value, $_{b}$ = maximum value
- Lognormal where: $(\mu, \sigma_{\cdot})$ μ' = mean of underlying normal distribution, σ' = standard deviation of underlying normal distribution

Appendix G

Improvement in Human Health Risk Assessment Utilizing Site- and Chemical-Specific Information: A Case Study

Del Pup, J.,[1] *Kmiecik, J.,*[2] *Smith, S.,*[3] *Reitman, F.*[1]

1.0 Introduction

The U.S. Environmental Protection Agency (EPA) has classified 1,3-butadiene (butadiene) as a B2 ("probable") human carcinogen.[4] Conservative screening level cancer risk estimates reported by EPA to rank sources and prioritize regulatory action associated emissions of butadiene from the Texaco Chemical Company, Port Neches, Texas facility with a maximum individual risk of 1 in 10. Although the agency emphasized that these screening level estimates should be viewed only as rough estimates of the relative risks posed by the facility under evaluation, and should not be interpreted to represent an absolute risk of developing cancer, the risk estimate generated a high level of concern. In this paper we provide a discussion of results of an effort to use site-specific data, species differences in the metabolism of butadiene, the Monte Carlo procedure, and other factors to estimate risk to the community. The effect of some of these factors is profound. For example, using this information, the range of risks at the closest residence is estimated to be 1 in 10,000,000 to 3 in 10,000. This range of

[1] Texaco, Inc.
[2] Texaco Chemical Company
[3] Radian Corporation
[4] EPA classifies chemicals for which there is sufficient evidence for carcinogenicity in experimental animals and inadequate or no evidence for carcinogenicity in humans as Group B2, "probable human carcinogens."

uncertainty is driven largely by species differences in butadiene uptake and metabolism used in the slope factor.

The purpose of this study is twofold:

1) to address the concern posed by the EPA screening level risk assessment by increasing the precision of estimates of the risks potentially posed by butadiene from the facility
2) to demonstrate a process whereby site specific data is utilized in place of regulatory default assumptions to provide a more scientifically credible estimate.

It is neither the intent of this paper to evaluate any cause and effect relationship between 1,3 butadiene exposure and cancer in humans, nor to provide the most scientifically defensible cancer potency estimates for 1,3-butadiene. Risks referred to in this paper are hypothetical estimates useful for regulatory purposes. These estimates assume as a matter of regulatory policy that a low-dose linear carcinogenic response to butadiene occurs in humans. Actual risks would be zero if butadiene is not carcinogenic to humans at these exposure levels.

Texaco initiated this evaluation in 1990 (Radian Corporation, 1990). That assessment focused on increasing the precision of the EPA screening level risk estimates based on more realistic representation of emissions, dispersion and exposure after completion of the Butadiene Modernization Project. This project centered around changing the extraction solvent used in the distillation process and in changing the "once-through" cooling water system to a recirculating cooling tower system in order to reduce butadiene emissions. Although based on site-specific information wherever possible, the risk assessment noted several sources of uncertainty that impacted interpretation of the risk estimates. Primary sources of uncertainty were identified as estimated emissions rates, assumptions and algorithms associated with dispersion modeling analysis, assumptions used to calculate inhalation exposure, and the theoretical estimate of the carcinogenic potency of butadiene, if any, in humans.

The Butadiene Modernization Project, now largely completed, has resulted in a process that is cleaner from both a product purity and environmental perspective. Butadiene emissions have been reduced more than 90 percent. Repeating the prior EPA screening level analysis predicts a maximum individual cancer risk after completion of this project in the range of 5-10 in 1000 based on a 70 year exposure to the maximum predicted annual-average ground level concentration 200 meters from the center of the plant. The current study was initiated to reexamine some of the sources of uncertainty in the risk estimates and to update the risk estimates, using the most site-specific and chemical-specific information available (Radian 1992a) The resulting risk estimates range from 3 in

10,000 to 1 in 10,000,000 at the nearest residence, which are much lower than EPA's original 1 in 10 risk estimate. In addition, we also provide estimates of risk to the nearest residence and school using the Monte Carlo analyses. These provide central tendencies which result in even lower estimates of risk.

The health risk analysis undertaken by the author improves upon the EPA-generated health risk assessment by reevaluating assumptions pertinent to determining the maximum exposed individual risk and risks at various locations in the community. Risks were characterized for the conventional "worst case" 70-year exposure, the 30-year upper bound exposure, the 9-year average residential exposure, and the 95th percentile fraction of life exposed (FLE) based on national human activity pattern distributions. Assumptions used in the development of the EPA-sanctioned unit risk factor for butadiene and impact on the magnitude of risk using alternate unit risk factor assumptions were also evaluated. The assessment also evaluated differences between ground-level concentrations predictions by the Industrial Source complex Long-Term (ISCLT) and the Industrial Source Complex Short-Term (ISCST) atmospheric dispersion models. In addition, results using two meteorological data sets for the area and various decay coefficients for butadiene were evaluated.

This study addresses many of the issues, assumptions, and uncertainties inherent to inhalation pathway risk assessments. However, it should be noted that the analyses, conducted for the current study are site-specific and, therefore, the results may not be applicable to other source configurations, meteorological data sets, or other receptor populations. The study is intended to illustrate a process by which human risk assessments can be improved by using available site-and chemical-specific information.

2.0 Emission Statements

The facility produces butadiene by solvent extraction from a crude C4 stream. The process involves distilling the extracted butadiene to remove heavy ends and final polishing to obtain a butadiene product with purity of 99.7%. Potential sources of butadiene emissions included equipment components in the process units, tank farms, and on the product loading racks; cooling towers; process flares; the dock flare; steam boilers; wastewater treatment plant; the cracking unit; and the butadiene sphere. The butadiene emission estimates were based primarily on actual process data and source-specific information, and on Air Control Board and/or EPA approved emission factors.

It is recognized there are other butadiene sources in the Port Neches area (e.g. butadiene emissions from other area facilities). These other sources of butadiene emissions were not included in the analysis.

3.0 Environmental Fate And Transport Modeling

Atmospheric fate and transport is usually assessed using a mathematical atmospheric dispersion model. Industrial Source Complex (ISC) Models are classified as "preferred" models in the EPA's "Guidelines on Air Quality Models (Revised), 1987 (EPA, 1987). Two versions of the ISC model are available. Both the Industrial Source Complex Short Term (ISCST) and the Industrial Source Complex Long-Term (ISCLT) model are steady state Gaussian plume models preferred for use with industrial complexes with flat terrain such as that found in the area of the facility.

3.1 Industrial Source Complex Model Comparisons

The ISCST model is designed for use in predicting concentrations using averaging periods from one hour to one year. This model utilizes discrete hourly meteorological data. The ISCLT model is designed for use in predicting annual-average concentrations. This model utilized meteorological data in the format of a STAR summary. The STAR summary is a joint-frequency distribution of wind speed, wind direction, and stability classification, processed from discrete hourly observations. The use of this meteorological data summary enables the ISCLT dispersion model program to calculate ambient concentrations much faster than ISCST because dispersion calculations are performed for a small number of meteorological categories rather than for every hour of the year. The ISCLT and ISCST use identical equations for calculating ambient concentrations, with the exception of several changes necessary for the incorporation of the STAR summary.

A model comparison using site-specific inputs revealed fairly good agreement between long-term and short-term results (Radian, 1992b). A 12.5% higher maximum off-property concentration was predicted using the long-term model, but the average concentration of all receptor locations predicted by both models were identical. Given the good agreement between the models, the requirement of evaluating butadiene for long-term or chronic effects, and the faster model execution time, the ISCLT was chosen for this analysis.

3.2 Effects of the use of Atmospheric Decay Coefficients in ISCLT

The ISCLT model provides a mechanism to account for pollutant removal by physical or chemical processes. There are three main chemical reactions which were considered important to evaluating atmospheric concentrations of butadiene, including: 1) reaction with hydroxyl radical (·OH);2) reaction with ozone (O_3); and reaction with nitrogen trioxide radical (·NO_3) (EPA, 1983). The reaction with ·OH is dominant during the day while reaction with ·NO_3 is dominant

at night. Ozone reactivity occurs during the day and night. All reactions are temperature dependent, with butadiene residence times being greater during the winter months and dependent on the chemical species available for reaction in the particular airshed of interest.

Annualized pollutant decay factors were developed by Radian Corporation for use with the ISCLT model based on site-specific temperatures and airshed data estimates. The decays were annualized to address the long-term or chronic exposure aspects of the study. Due to the low solubility of butadiene, physical removal processes such as pollutant incorporation into clouds and rain were not considered to be important pollutant degradation processes and were not considered in this analysis.

Figures 3-1, 3-2, 3-3, and 3-4 illustrate concentration isopleths for no decay, low decay, median decay, and high decay of butadiene, respectively. These results indicate that the inclusion of pollution decay in the transport and fate analysis of butadiene has only minimal effects on predicted ground-level concentrations near the facility. However, as distance from the facility increases, inclusion of butadiene decay in the fate and transport analysis significantly decreases predicted ground-level concentrations.

3.3 Alternative Meteorological Data Set Comparison for the ISCLT Model

Two quality-assured sets of meteorological data were evaluated for use in this analysis: 1) a 14-year composite annual joint frequency distribution of wind speed, wind direction, and stability class (STAR) data processed from the National Weather Service (NWS) hourly surface observations at the County Airport, located approximately four miles from the plant boundary; and 2) a two-year composite STAR data set processed from 1990 and 1991 Regional Planning Commission (RPC) continuous observations at another County Airport location, approximately three miles form the plant boundary. The RPC data were selected for use in the majority of the analyses due to the continuous nature of the observations and the use of measured mixing heights. However, to examine the sensitivity of the risk estimates to changes in the meteorological data set, the ISCLT dispersion model was run with identical inputs, varying only the meteorological data. At nearby locations, predicted concentrations using RPC data were 25 to 100% higher than predicted concentrators using the NWS data. Using the RPC data, concentrator isopleths would extend farther to the east and are more rounded. using the NWS data, the isopleths would show more of a northsouth bias (Radian, 1992a).

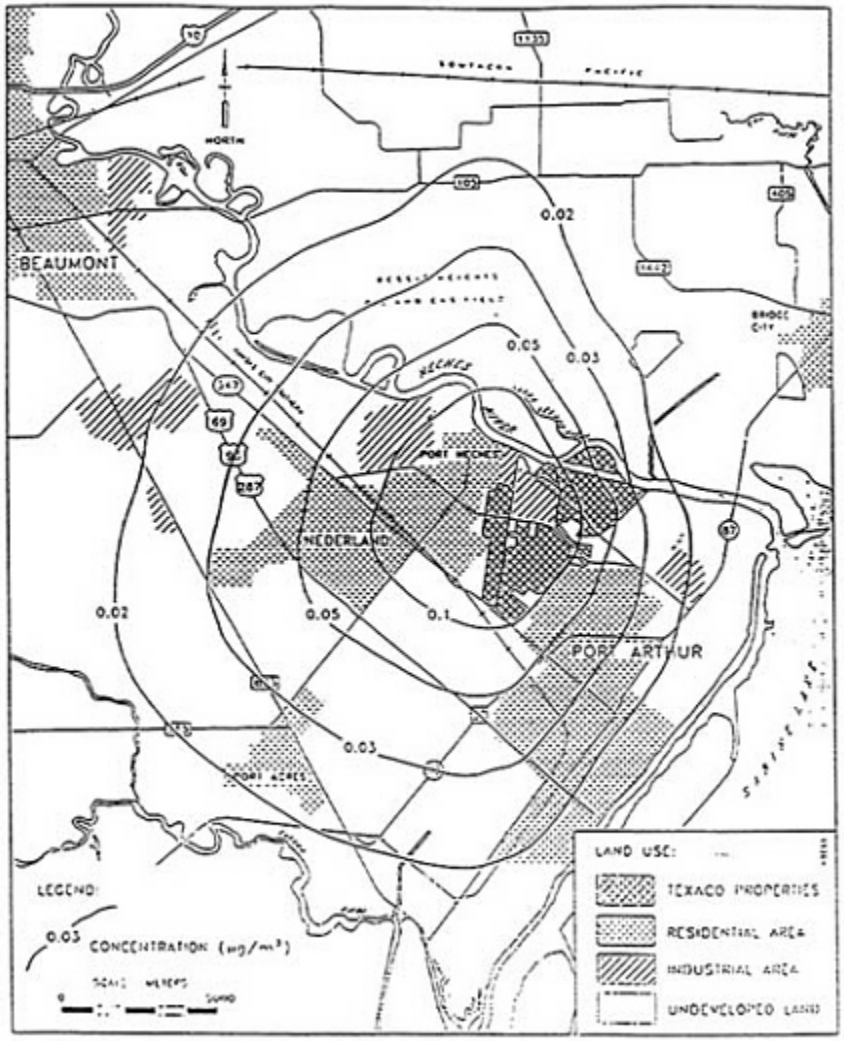

FIGURE 3-1 Concentration Isopleths (µg/m^3). No Butadiene Decay

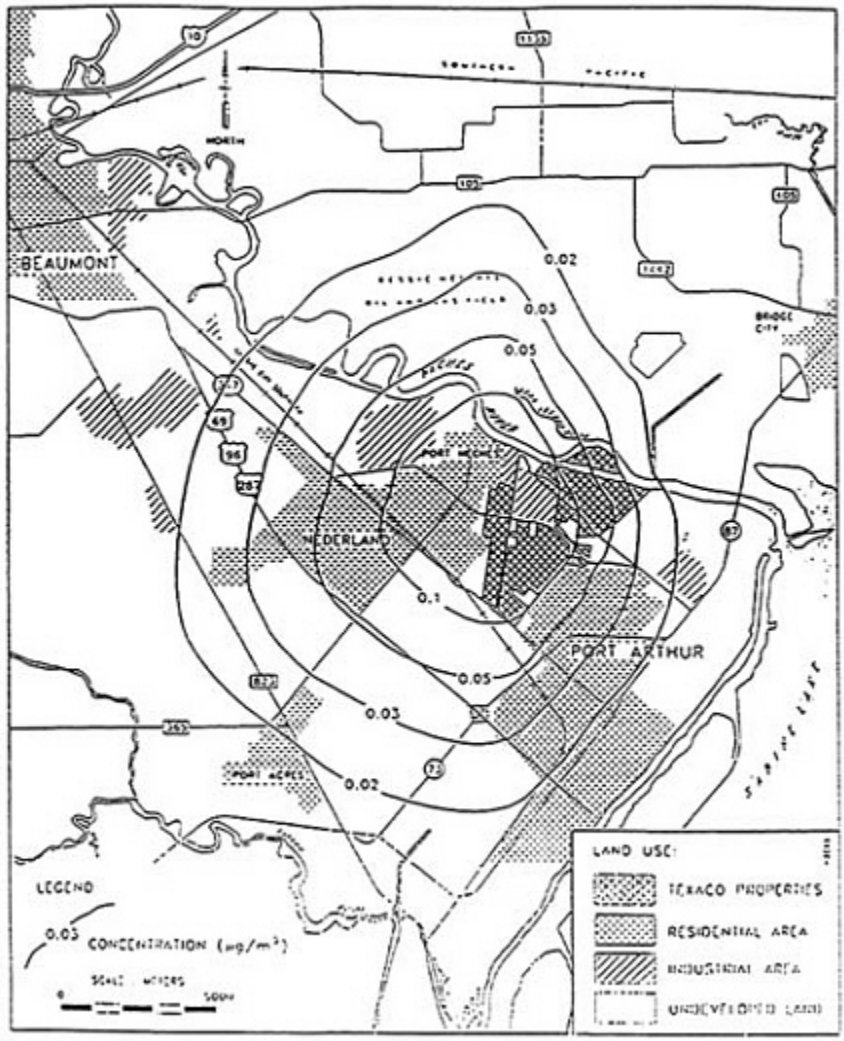

FIGURE 3-2 Concentration Isopleths (μg/m^3). Low Butadiene Decay

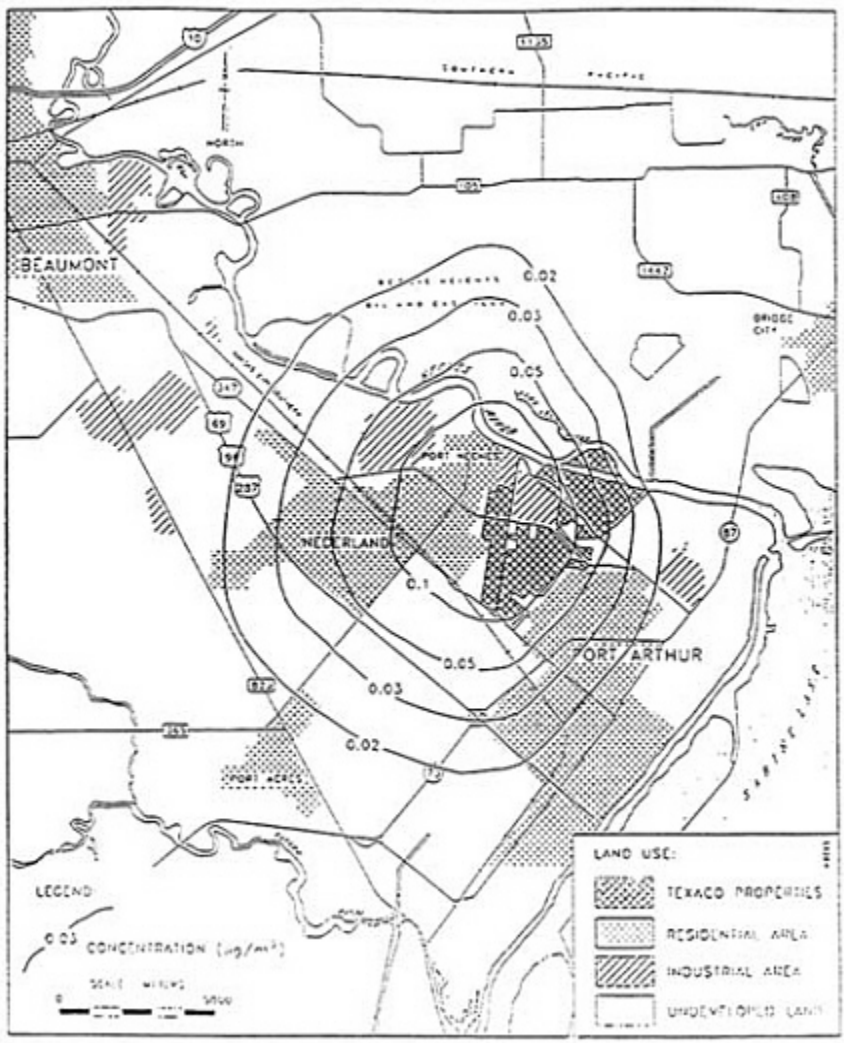

FIGURE 3-3 Concentration Isopleths (µg/m^3). Median Butadiene Decay

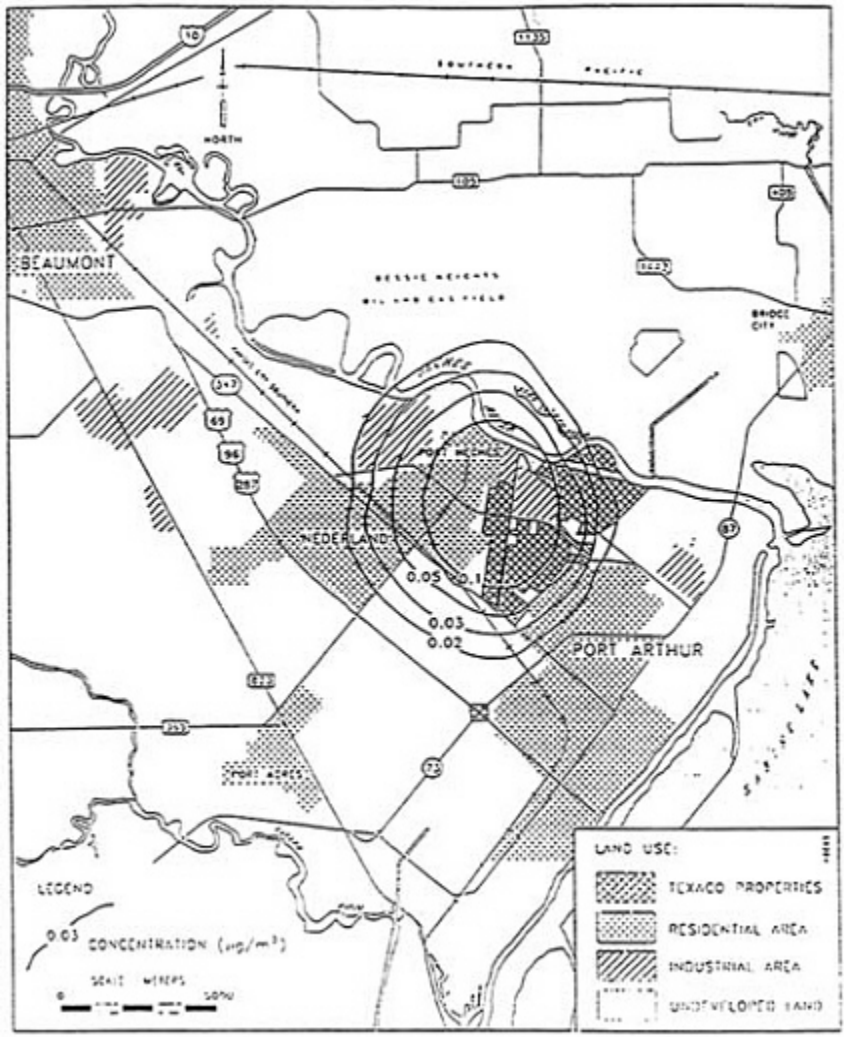

FIGURE 3-4 Concentration Isopleths (μg/m^3). High Butadiene Decay

4.0 Human Health Assessment

Risk characterization involves integrating exposure and toxicity information into quantitative and qualitative expressions of potential health risk. For potential carcinogens such as butadiene, risk can be characterized by estimating the potential for carcinogenic effects or by estimated ambient air concentration with health-based ambient guidelines or standards.

To characterize potential carcinogenic effects, estimated risks that an individual will develop cancer over a lifetime of exposure to butadiene were calculated from projected intakes and the cancer slope factor. The cancer slope factor converts estimated daily intakes directly to an estimate of incremental risk as follows:

$$\text{Dose (mg/kg-day)} \times \text{Cancer Slope Factor (mg/kg-day)}^{-1} = \text{Lifetime Excess Cancer Risk}$$

The slope is often an upper 95th percentile confidence limit of the probability of response based upon experimental animal data and an assumption of linearity in the low-dose portion of dose-response curve. Therefore, the carcinogenic risk estimate will generally be an upper-bound estimate, indicating that the "true-risk", if any, will probably not exceed the risk estimates based on the slope factor and is likely to be less than that predicted.

Individuals may be exposed to chemical in air by inhalation of chemicals in the vapor phase or adsorbed to particulate. Dermal absorption of vapor phase chemicals such as butadiene is considered to be lower than inhalation intakes and, therefore, was not quantified in this risk assessment (EPA, 1989). Inhalation of airborne vapor-phase chemicals can be quantified using the following formula:

$$\text{Intake (mg/kg-day)} = \frac{CA \times IR \times ET \times EF \times ED}{BW \times AT}$$

where: CA = Contamination Concentration in Air (mg/m^3);

IR = Inhalation Rate (m^3/hour);

ET = Exposure Time (hours/day);

EF = Exposure Frequency (days/year);

ED = Exposure Duration (years);

BW = Body Weight (kg); and

AT = Average Time (period over which exposure is averaged—days)

Lifetime exposure must be evaluated to determine cancer risk. To provide a conservative analysis of lifetime community exposure, the exposed population (represented by an average 70 kg adult) has been assumed to inhale (at an average rate of 20 m^3/day) predicted ground-level concentrations continuously, 24

hours/day, 365 days/year, for a 70 year exposure duration. More recently, EPA has employed "reasonable maximum" assumptions of 24 hours/day, 350 days/ year for 30 years.

4.1 Characterization of Risk

To characterize the risks, both the health variables and the exposure variables were combined under three scenarios, the Base Case, Worst Case and Best Case (Table 4.1). For example, the Worst Case includes inputs that reflect a highly conservative approach whereas the Base Case and Best Case make use of different levels of sophistication in the utilization of site-specific data, exposure assumptions, and recent biological data on the uptake and metabolism of butadiene.

The ISCLT model calculates an ambient concentration at each point (or receptor) provided in the model input. Receptor placement was designed to identify the location of the maximum off-property concentration. Additional receptors were also placed at the nearest residences and the nearest school complexes in several directions. Therefore, concentrations at several locations of special interest were determined. Table 4-2 summarizes the Base Case maximum individual risk calculations for each of the nearby receptor locations. Risk estimates at the closest residences were 1 in 10,000. Risk estimates at the location of maximum off-property concentration were about 5 times higher. Estimated risks at the school locations were lower, ranging from 7 in 100,000 to 4 in 1,000,000. This can be compared with the approximate 1 in 4 background risk of developing fatal cancer in the U.S. population (Harvard School of Public Health, 1992). Refinements to this assessment were made by evaluating additional variables impacting on the risk estimates. Some of these, particularly the slope factor, have a high level of uncertainty.

4.1.1 Effect of Exposure Assumptions

Realistically, very few people remain in the same location for a lifetime. To account for exposure durations less than a lifetime, the following formula can be used to quantify the Lifetime Average Daily Exposure (LADE) (Price et al.1991):

$$\text{LADE (mg/kg-day)} = \frac{\text{CA} \times \text{IR} \times \text{FLE}}{\text{BW}}$$

where:CA = Contaminant Concentration in Air (mg/m^3);

IR = Inhalation rate (m^3/day);

FLE = Fraction of Life Exposed (unitless); and

BW = Body Weight (kg)

TABLE 4-1 KEY VARIABLES THAT DESCRIBE THREE CASES

Variables	Base Case	Worst Case	Best Case
Meteorological Data			
1 SETPC	√	√	√
2 NWS			√
Butadiene Decay			
1. No Decay		√	
2. Low Decay			
3. Medium Decay	√		
4. High Decay			√
Exposure Assumptions			
1. Traditional Worst Case (24 hrs/day, 365 days/yr for 70 yrs)		√	
2. Reasonable Maximum (24hrs/day, 350 days/yr for 30 yrs)[1]	√		
3. 95th Percentile Fraction of Life Exposed (based on national human activity pattern distributions)			
4. Average Fraction of Life Exposure (based on national human activity pattern distributions)			√
Butadiene Slope Factor			
1. EPA Slope Factor	√	√	
2. EPA Slope Factor Adjusted by a Factor of 30			
3. EPA slope Factor Adjusted by a Factor of 590			√

[1] As defined by U.S. EPA, 1989

National statistics are available on the upper-bound (30 years) and average (9 years) number of years spent by individuals at one residence (EPA 1989, 1991). The "upper-bound" value was used as the exposure duration when calculating the reasonable maximum residential exposures. An exposure frequency of 350 days/year was used, assuming 15 days/year are spent away from home. Assuming a 70 year lifetime, the FLE is an average of 0.12 and a reasonable maximum of 0.41.

A Point Source Exposure Model (PSEM) was used to characterize the distribution

TABLE 4-2 ESTIMATED MAXIMUM INDIVIDUAL CANCER RISK AT IDENTIFIED RECEPTOR LOCATIONS FOR THE BASE CASE.

RECEPTOR LOCATION[a]	MAXIMUM INDIVIDUAL CANCER RISK FOR THE BASE CASE[b,c,d]
Off Property Max (West Property Line)	5E-04 (5 in 10,000)
Residence 1	1E-04 (1 in 10,000)
Residence 2	1E-04 (1 in 10,000)
School 1	5E-05 (5 in 100,000)
School 2	7E-05 (7 in 100,000)
School 3	5E-06 (5 in 1,000,000)
School 4	4E-06 (4 in 1,000,000)

[a] The location of these receptors in relation to the facility is identified in Figure 3-1
[b] Based on EPA "reasonable maximum" inhalation exposures (EPA, 1989) and the EPA potency slope of 1.8 $(mg/kg\text{-}day)^{-1}$. Reasonable maximum exposure assumptions based on residential exposure patterns are assumed at all locations.
[c] Range of risks from zero to stated value
[d] Backround fatal cancer risk in the U.S. is approximately 1 in 4.

of exposures received over a long-term period based on information on mobility, mortality, and daily activity patterns (Price et al 1991). PSEM models the time of residence in the zone of impact and the amount of time spent at home as variables that yield a probability density function for the FLE. The model predicted that, on average, individuals live in their current house for 16.5 years and spend 18 hours per day at home. The average value of the FLE calculated by PSEM using national statistics was 0.16. The median value was 0.12, and the 95^{th} percentile of the distribution was 0.42. Inhalation exposures for all receptor locations were calculated based on residential exposure assumptions, using these FLE values. It is assumed for this report that 1,3-butadiene concentrations are the same inside and outside the home. No attempt has been made here to validate this assumption.

Several exposure scenarios were examined in this assessment including: 1) "worst case" (24 hours/day, 365 days/year for 70 years); 2) "reasonable maximum" (24 hours/day, 350 days/year for 30 years); 3) 95^{th} percentile FLE based on national human activity pattern distributions, and 4) average FLE based on national human activity pattern distributions. Figure 4-1, 4-2, and 4-3 illustrate the areal extent encompassed by several risk levels using traditional "worst case", reasonably maximum, and average exposure assumptions. As indicated in the figures, the areal extent encompassed by specific risk levels is very sensitive to changes in the time, frequency, and duration of exposure.

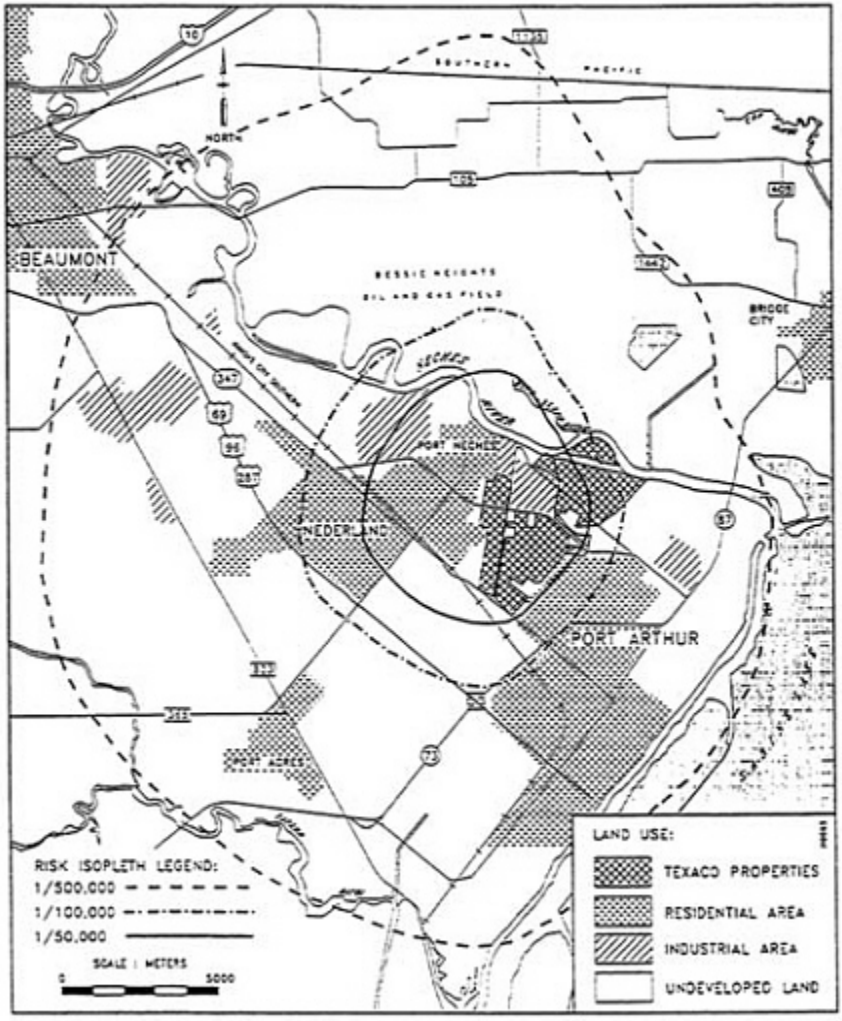

FIGURE 4-1 Area Encompassed by Specific Risk Levels-Traditional Worst Case Exposure Assumptions

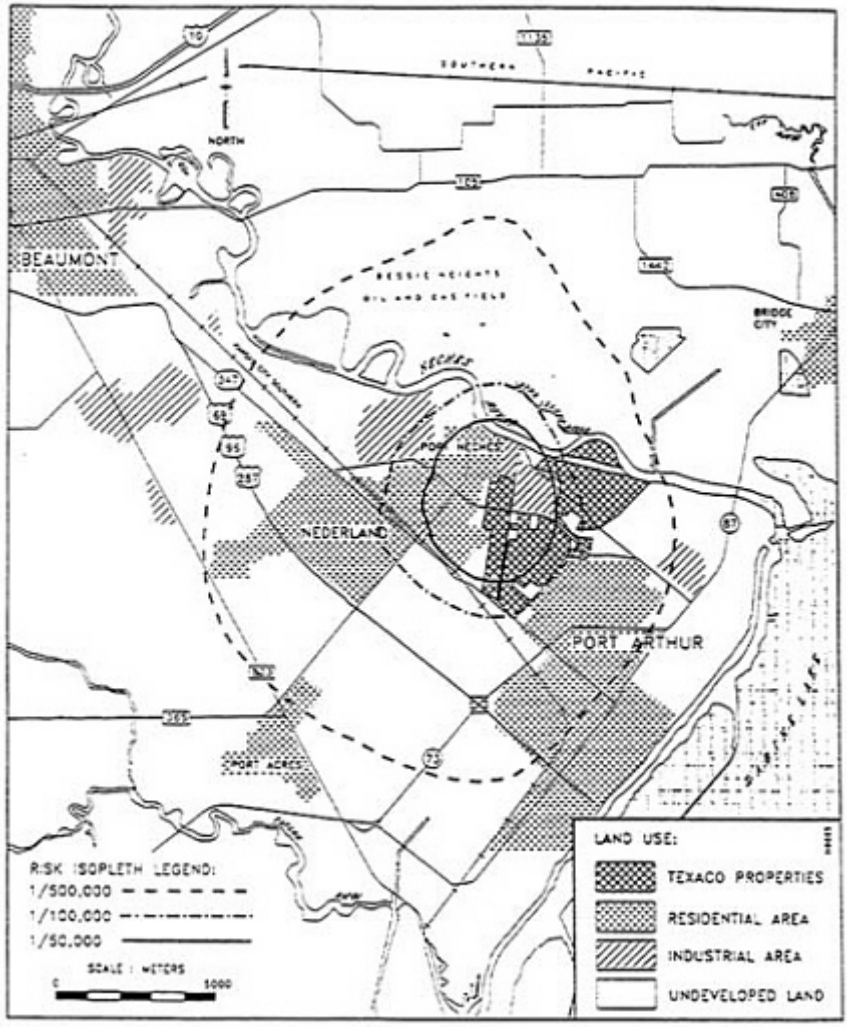

FIGURE 4-2 Area Encompassed by Specific Risk Levels-Reasonable Maximum Exposure Assumptions (Base Case)

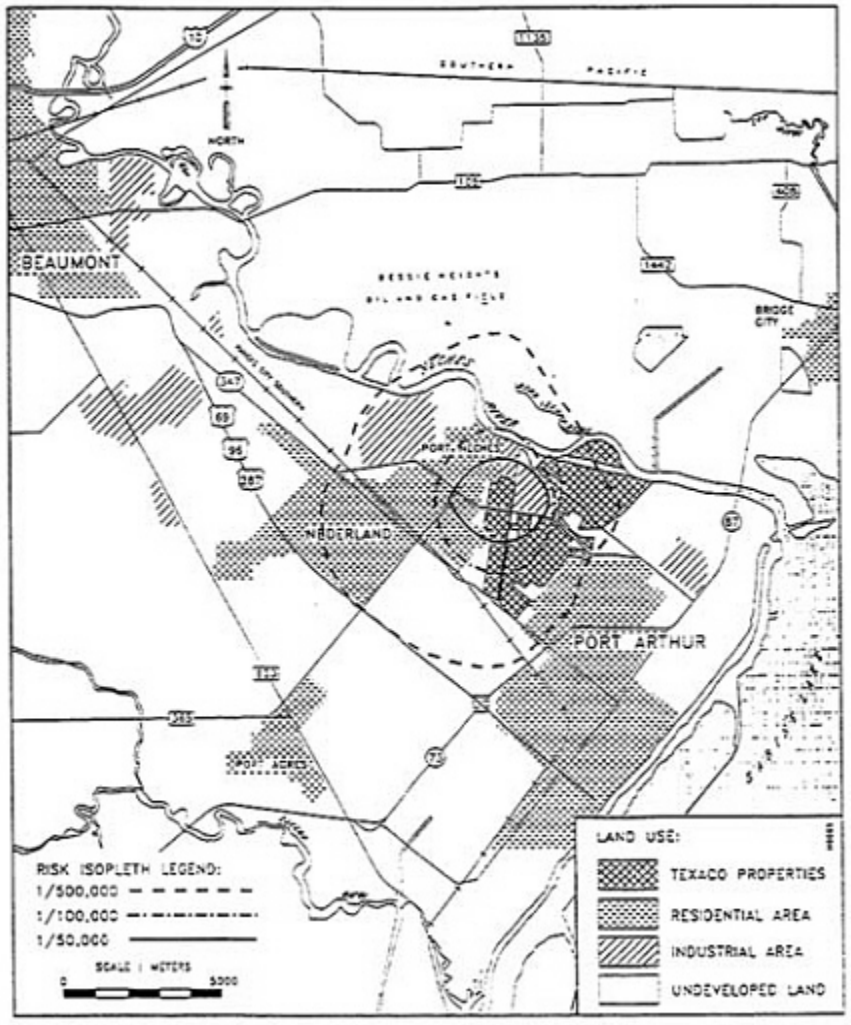

FIGURE 4-3. Area Encompassed by Specific Risk Levels-Average Exposure Assumptions

4.1.2 Effect of Cancer Slope Factor Assumptions

The EPA-sanctioned slope factor for butadiene of 1.8 $(mg/kg\text{-}day)^{-1}$ was used in all previous analyses (IRIS 1992). In the current analysis, however, risk estimates were also generated using alternative slope factors based on research that the EPA slope factor may overpredict risks to the human population.[5] Cancer slope factors can be converted to unit risk estimates to determine the risk per unit air or water concentration. The inhalation unit risk can be calculated by dividing the slope factor by 70 kg (average body weight for an adult) and multiplying by 20 m^3/day (adult average inhalation rate) assuming a 70 year exposure period (EPA 1989, 1991).

EPA calculated in inhalation risk estimate for butadiene of 2.8-04 $(\mu g/m^3)^{-1}$, based on an absorption factor of 54%, which was derived from preliminary results of an absorption study conducted in mice and sponsored by the National Toxicology Program (NTP). The procedure for determining animal-to-equivalent human dose was adjusted to account for the fact that at high concentrations, the internal dose (mg/kg) is not directly proportional to external concentrations. A final report of the NTP study has been published and differs significantly from the preliminary results (Bond et al. 1986). Results from the final report suggested that butadiene retention by mice in the initial study may have been overestimated by a factor of five. Based on these data, risk estimates derived using EPA-sanctioned values for butadiene should be adjusted downward by approximately a factor of five. Based on the discussion published in EPA's Integrated risk Information System (IRIS, 1992), EPA used an absorption factor of 54% in calculating a slope factor. IRIS states that differences between the retention of butadiene reported in the initial and final study have been accounted for in EPA's calculations. Assuming this is correct, there is no need to make adjustments in risk estimates based on the EPA value. However, the animal upper-limit slope factors are identical to those published by the EPA in 1985, suggesting that this correction has not been made (EPA, 1985). If the correction was not made, the downward adjustment by a factor of five is appropriate.

The respiratory systems of humans differ from experimental animals in many ways. These differences result in variations in air flow, deposition of inhaled agents, as well as the retention of that agent. The dose of partially soluble vapors, such as butadiene, is proportional to oxygen consumption. Oxygen consumption is, in turn, proportional to (body weight) and is also proportional to the

[5] A cohort epidemiologic study of workers employed at this facility between 1943 and 1979 showed a statistically significant deficit for all causes of death and all cancers. There was, however, a statistically significant excess of deaths from lymphosarcoma. This was concentrated in workers employed less than 10 years and first employed prior to 1946 (Divine, 1990).

solubility of the gas in body fluids, which is expressed as an absorption coefficient for the gas. In the absence of experimental evidence to the contrary, the absorption coefficient is assumed to be the same for all species. Therefore, butadiene exposure concentrations (in ppm) used in animal studies were assumed to be equivalent to the same concentration in humans. However, smaller animals have higher minute respiratory volumes per unit of body weight to supply their relatively larger requirements for oxygen. Since the dose of butadiene (by inhalation) is proportional to oxygen consumption, species with higher minute respiratory volumes would be expected to have larger body burden of the chemical.

Studies have been conducted which indicate that nonhuman primates absorb considerably less butadiene than mice (Dahl et al. 1990). At 10 ppm, mice retain approximately 6.6-fold more butadiene than monkeys. The human species is much more closely related to the monkey than the mouse, both physically and anatomically. Therefore, primate retention data should be used as a basis for estimating retention by humans. On this basis, risk estimates derived from EPA sanctioned toxicity values should be adjusted downward by a factor of six.

In quantitative risk modeling, internal concentrations of butadiene were used as a measure of dose. However, in doing so, species differences in metabolism of butadiene were ignored. In studies sponsored by NTP (Dahl et al. 1990), mice were shown to attain approximately 590-fold higher blood levels of the monoepoxide (a DNA-reactive and mutagenic metabolite of butadiene, assumed to be a toxic metabolite) than did primates.[6] Based on the assumption that humans metabolize butadiene in a manner that is more closely related to nonhuman primates, humans should be approximately 590-fold less sensitive to butadiene's carcinogenic effects than mice. Therefore, estimates of risk should be adjusted by a factor of 590 to account for species differences in metabolism of butadiene. Use of the internal concentration of the monoepoxide would obviate the need to adjust for difference in retention of inhaled butadiene.

The available comparative studies suggest that the equivalent potency of butadiene in humans could be substantially less than that used as the basis for EPA's calculated cancer slope factor. Based on the available data, the slope factor could be adjusted downward (i.e., to indicate lower potency for humans) by a factor of 30 (5 × 6 based on current retention data for the mouse and mouse/primate differences in retention) to 590 (based on mouse/primate differences in blood levels of the monoepoxide). Since risks change proportionally to changes in the butadiene slope factor, the risks using the alternative slope factors are lowered by a factor of 30 to 590. Figures 4-4. 4-5 and 4-6 illustrate the way in

[6] Metabolites were tentatively identified, based on co-distillation with standards.

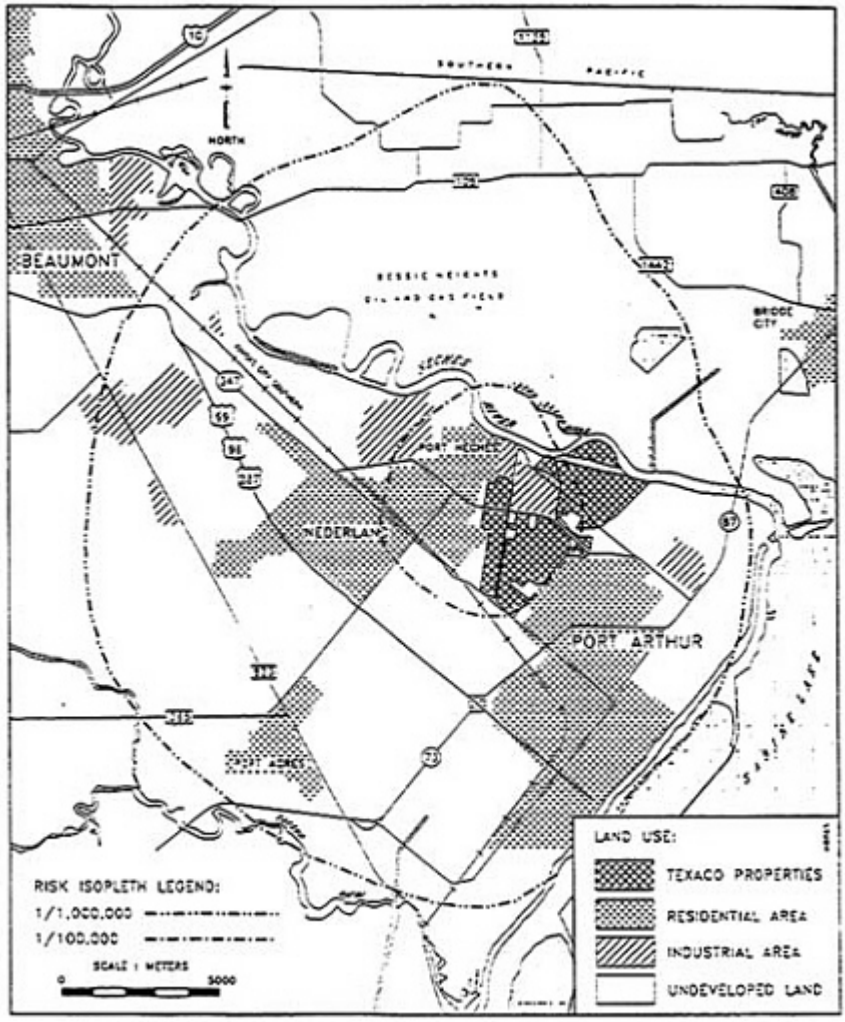

FIGURE 4-4. Area Encompassed by Specific Risk Levels-EPA Slope Factor (Base Case)

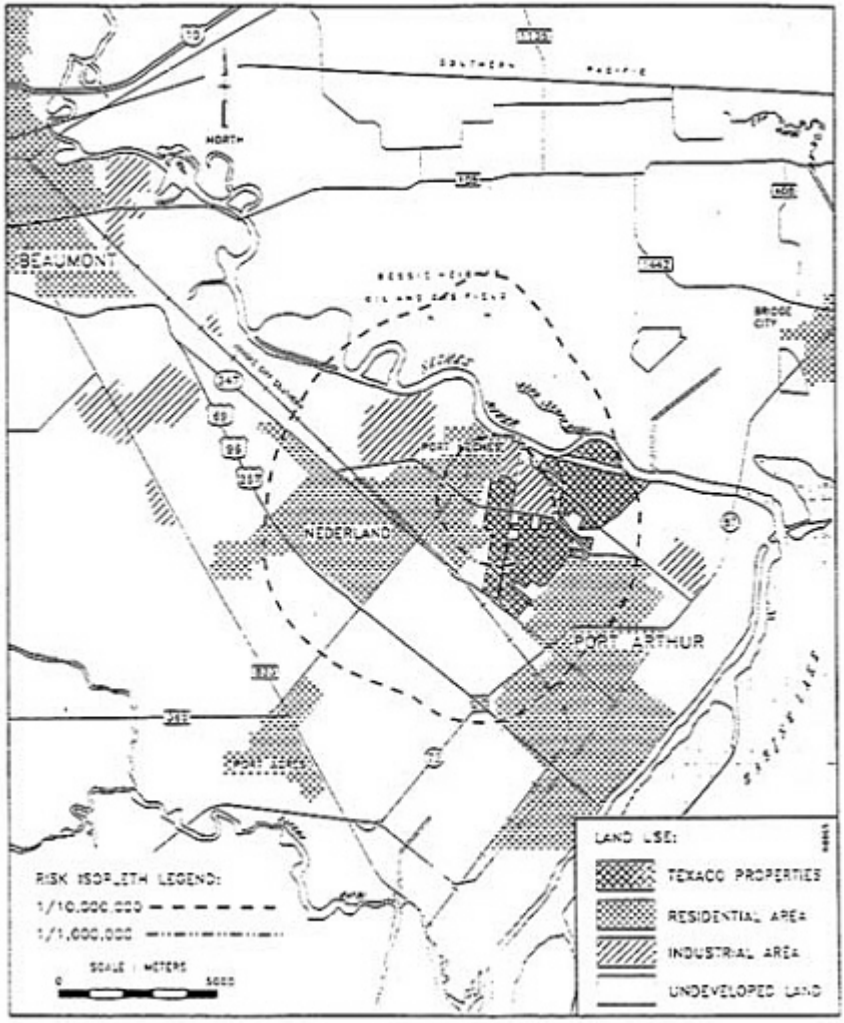

FIGURE 4-5. Area Encompassed by Specific Risk Levels-EPA Slope Factor Adjusted by a Factor of 30

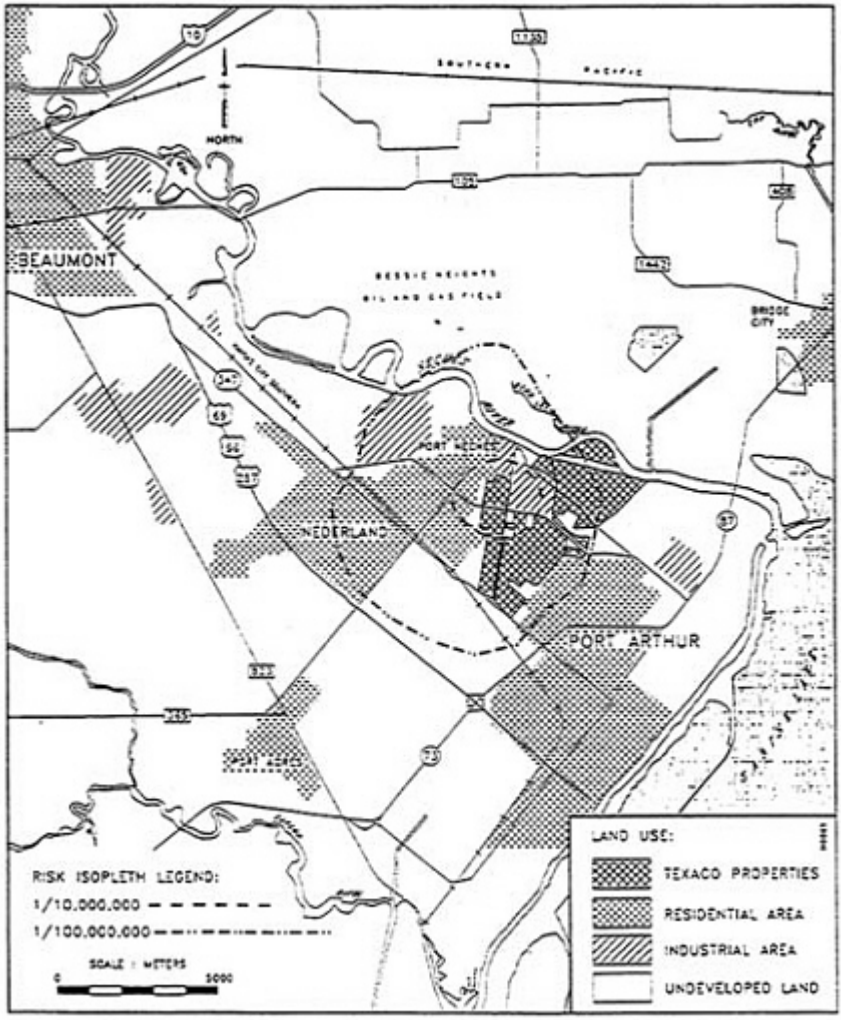

FIGURE 4-6. Area Encompassed by Specific Risk Levels-EPA Slope Factor Adjusted by a Factor of 590

which changes in the butadiene slope factor affect the area encompassed by specific risk levels.

5.0 Probabilistic Monte Carlo Simulation

Risk estimates resulting from a series of "worst case" assumptions can be expected to overestimate actual risk. However, there is no way for the regulator, industry representatives, the potentially exposed population, or other interested parties to interpret the degree of conservatism. EPA risk assessments are expected to address the range of risk including the central tendency and high end portion of the risk distribution (EPA, 1992). In addition, they are expected to include a statement of confidence in the risk assessment itself. Stochastic analysis of risk provides a distribution of estimated risks based on the use of probability density functions for input parameters instead of single point estimates.

Monte Carlo simulation calculates risk through numerous iterations using randomly generated values from the defines probability functions. The resulting distribution of risk estimates makes greater use of the scientific evidence and data related to exposure and theoretical risk without sacrificing conservatism. Monte Carlo avoids compounding of "worst case" assumptions and uncertainty, and provides quantitative information on the uncertainty in the risk values.

The shape of the distribution and the range between low and high end estimates portray the uncertainties incorporated in the assessment and can be used to interpret the level of confidence in the assessment. A narrow range between 5^{th} and 95^{th} percentile of the distribution implies a low level of overall uncertainty and, consequently, a high level of confidence in the assessment. A broad range implies a high level of uncertainty.

In this assessment, the range in the risk estimates from the 5^{th} and 95^{th} percentile at the closest residence was 4 in 100,000,000 to 2 in 10,000 (Radian, 1992b). This range spans almost four orders of magnitude, indicating a very high level of uncertainty. The range in estimated risk from the 5^{th} to the 95^{th} percentile at the closest schools was 5 in 10,000,000,000 to 6 in 1,000,000. This range spans more than four orders of magnitude. The slightly greater span in the risk range at this location results form the greater potential influence of butadiene decay in the atmosphere as the distance from the facility increases. Therefore, the level of confidence in the estimates of risk associated with butadiene at the facility can only be described as low.

6.0 Conclusions

A number of variables examined in this risk assessment significantly impacted the final theoretical risk estimates. These variables included: 1) the meteorological data used in transport and fate modeling; 2) butadiene decay factors; 3) exposure time, frequency, and duration; and 4) the slope factor for butadiene.

Base Case estimates were developed including inputs for key variables that are relatively conservative. The sensitivity of Base Case estimates to varying inputs for these key variables was evaluated. The Base Case predicted risks in the range of 1 in 10,000 at the nearest residences, and 4 in 1,000,000 to 7 in 100,000 at the nearest schools. Worst Case estimates were only two to three times higher than Base Case estimates.

Best Case estimates, which provide an additional measure of the level of uncertainty associated with the estimates, ranged from more than three to four orders of magnitude lower than Worst Case estimates. The butadiene slope factor contributes almost three orders of magnitude to the theoretical risk estimates separating the Worst Case and Best Case scenarios. While the butadiene decay factor did not significantly affect the risk estimates at nearby locations, this effect was location dependent. The Base Case risk estimates (1 in 10,000 at the nearest residences) represents an upper-bound to the risk associated with the butadiene emissions from the facility. The "true risk" is unlikely to be higher, and is most likely lower. An examination of some of the key variables that influence estimates of theoretical risk indicates that the maximum individual risk at the nearest residences may be as low as 1 in 10,000,000. Risk estimates in this report should be considered in comparison to the approximate 1 in 4 background fatal cancer risk in the U.S. population. In all cases the risk would be zero if butadiene is not carcinogenic in humans at prevailing exposure levels.

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Appendix H-1

Some Definitional Concerns About Variability

Each of the three major types of variability (temporal, spatial, and interindividual) can be characterized in three ways, as follows (these examples are all related to human variability in susceptibility, although other examples are possible):

- Variability is (or can be modeled sufficiently precisely as though it were) is) either *discrete* or *continuous*. For example, albinos are many times more sensitive to sunlight than other members of the population, so a (dichotomous) discrete assumption might well be appropriate here. In contrast, because body weights vary continuously, the cancer risk per unit dose of a substance cannot be modeled dichotomously without the loss of much of information.
- Variability is *identifiable* or *unidentifiable*. Albinism is a good example of identifiable variability, whereas the extent of a person's ability to detoxify a particular active metabolic intermediate might not be discernible without invasive testing, and hence is unidentifiable for most of the population.
- Identifiable variability is *dependent* on or *independent of* additional variable characteristics that society deems salient. For example, some factors that cause genetic predisposition to the carcinogenic effect of chemicals are correlated with race, sex, or age. If society deems that those who are predisposed already deserve special attention because of the other factors, the importance of the variability is heightened. But some kinds of identifiable variability, such as body weight and phenylketonuria, are more "value-neutral" or are uncorrelated with any relevant characteristic.

Appendix H-2

Individual Susceptibility Factors

One way to categorize the many different factors that affect susceptibility to cancer is to divide them into qualitatively different classes along two strata—according to the prevalence of each factor in the human population and according to the degree to which the factor can alter susceptibility. Finkel (1987) noted that most of the factors that are very common (Table H-1) tend to confer only marginal increases in relative risk on those affected (less than a doubling of susceptibility). Many of the other predisposing factors, long recognized as conferring extremely high relative risks, also tend to be quite uncommon (see Table H-2).

However, several important determinants of cancer susceptibility might well be neither rare nor of minor importance to people, and some speculate that this might be quite important for societal risk assessment. This section discusses five factors that might be among the most significant.

Carcinogen Metabolism

Most chemical carcinogens require metabolic activation to exert their oncogenic effects, and the amount of carcinogen produced depends on the action of competing activation and detoxification pathways,. Interindividual variation in carcinogen metabolism is therefore an important determinant of cancer susceptibility.

Chemical carcinogens are metabolized by a wide variety of soluble and membrane-bound enzymes. Multiple forms of human cytochrome P450 (CYP) are involved in the oxidative metabolism of chemical carcinogens, such as polycyclic

TABLE H-1 Examples of Common Predisposing Factors

Predisposing Factor	Mechanism Influencing Susceptibility to Cancer
A. Temporal Factors[a]	
• Circadian rhythms	
• Changing ingestion and inhalation characteristics during life	
• Depression and stress	
B. Nutritional Factors[b]	
• Vitamin A and iron deficiencies	May increase susceptibility to carcinogenic hydrocarbons
• Dietary-fiber intake	Insufficient intake may increase residence time of carcinogens in contact with epithelium of digestive tract
• Alcohol intake	May affect susceptibility through effect on liver
C. Concurrent Diseases[c]	
• Respiratory tract infections and bronchitis	May predispose lungs to cancer by disturbing pulmonary clearance or promoting scarring
• Viral diseases, e.g., Hepatitis B	May activate proto-oncogenes and cause liver necrosis and regeneration
• Hypertension	May increase the potential for DNA damage in peripheral lymphocytes

[a] Data from Fraumeni, 1975; Borysenko, 1987.
[b] Data from Calabrese, 1978.
[c] Data from Warren and Weinstock, 1987.

aromatic hydrocarbons (PAHs). Interindividual variation by a factor of several thousand has been observed in placental aryl hydrocarbon hydroxylase (AHH) activity, which is catalyzed by CYP1A1; some of this variability is under direct genetic control, but variations also result from an enzyme induction process due to maternal exposure to environmental carcinogens, such as tobacco smoke. A genetic polymorphism in CYP1A1 in which an amino acid substitution in the heme-binding region of the protein increases catalytic activity of PAHs has been linked to enhanced susceptibility to squamous cell carcinoma of the lung in cigarette-smokers (Nakachi et al., 1991). Japanese with the susceptible

TABLE H-2 Examples of Rare Predisposing Factors[a]

Predisposing Factor	Mechanism Influencing Susceptibility to Cancer
• Ataxia-telangiectasia	Chromosomal fragility, causing sensitivity to agents that increase genetic recombination
• Bloom's syndrome	Hypermutability
• Chediak-Higashi syndrome	Depletion of "natural killer" cells that combat incipient malignancies
• Down's syndrome trisomy 21	Tenfold excess leukemia risk
• Duncan's disease	Lymphoma in those infected by Epstein-Barr virus
• Epidermodysplasia verruciformis	Skin carcinoma associated with chronic infection with human papilloma virus
• Familial polyposis coli	Mutation in APC tumor suppressor gene leads to benign colonic growths that are predisposed to malignant transformation
• Fanconi's anemia	Possible deficiency of enzymes that scavenge active oxidizing species
• Glutathione reductase deficiency	Very high excess risk of leukemia
• Hereditary retinoblastoma	Predisposition to retinal cancer due to mutation of one allele of a tumor suppressor gene
• Li-Fraumeni syndrome	Germline mutation in the p53 tumor suppressor gene predisposes to multiple carcinomas and sarcomas
• X-linked agammaglobulinemia	Immune deficiency, predisposing to leukemia
• Xeroderma pigmentosum	Inability to repair some kinds of DNA damage, predisposing to skin cancer caused by ultraviolet radiation

[a] Data from Swift et al., 1991; Orth, 1986; Kinzler et al., 1991; Nishisho et al., 1991; Groden et al., 1991; Cleaver, 1968; Friend et al., 1986; Harris, 1989.

genotype had an odds ratio of 7.3 (95% confidence interval, 2.1-25.1) at a low level of cigarette-smoking; the difference in susceptibility between genotypes was diminished at high levels of smoking, and that suggests that interindividual variation may be especially important for risk-assessment purposes when "low" exposures are involved. The frequencies of this and other genetic polymorphisms

of enzymes involved in carcinogen metabolism may vary among ethnic groups.

CYP2D6 activity is polymorphic and has been linked to lung-cancer risk (Ayesh et al., 1984; Caporaso et al., 1990). CYP2D6 hydroxylates xenobiotics, such as debrisoquine (an antihypertensive drug) and a tobacco-specific *N*-nitrosamine. A person's polymorphic phenotype is inherited in an autosomal recessive manner. The rate of 4-hydroxylation of debrisoquine varies by a factor of several thousand, and lung-, liver-, or advanced bladder-cancer patients are more likely to have the extensive-hydroxylator phenotype than noncancer controls. In a case-control study of lung cancer in the United States (Caporaso et al., 1990), the extensive-hydroxylator phenotype had a greater cancer risk (odds ratio, 6.1; 95% confidence interval, 2.2-17.1) than poor-hydroxylator phenotype. The increase in risk was primarily for histologic types other than adenocarcinoma. British workers who have the extensive-hydroxylator phenotype and who are exposed to high amounts of asbestos or PAHs have an increased risk of lung cancer (odds ratio, 18.4; 95% confidence interval, 4.6-74 and 35.3; 95% confidence interval, 3.9-317, respectively) (Table H-3) (Caporaso et al., 1989). CYP2D6 might activate chemical carcinogens in tobacco smoke, such as some *N*-nitrosamines, or perhaps inactivate nicotine, the addictive component of tobacco smoke, so as to decrease its steady-state concentration and lead to an increase in smoking. A person with the extensive-hydroxylator phenotype might thus be at greater cancer risk. Another hypothesis is that an allele of the CYP2D6 gene is in linkage disequilibrium with another gene that influences cancer susceptibility.

The *N*-acetylation polymorphism is controlled by two autosomal alleles at a single locus in which rapid acetylation is the dominant trait and slow acetylation the recessive trait. Both slow acetylation and rapid acetylation of carcinogenic aromatic amines have been proposed as cancer risk factors. The slow-acetylator phenotype has been linked to occupationally induced bladder cancer in dye workers exposed to large amounts of *N*-substituted aryl compounds (Cartwright et al., 1982). The rapid-acetylator phenotype was more common in two of three studies of colon-cancer cases (Lang et al., 1986; Ladero et al., 1991; Ilett et al., 1987).

Wide interindividual differences in enzymes that detoxify carcinogens are also found. For example, competing detoxifying enzymes are found at each step in the metabolic pathway of benzo[a]pyrene activation to electrophilic diol-epoxides. A recent study of several of the enzymes involved in benzo[a]pyrene metabolism confirmed previous observations by showing a more than 10-fold person-to-person variation in enzyme activities and presented indirect evidence that tobacco smoke induced many of these enzymes (Petruzzelli et al., 1988). Genetic control of the presumed detoxification of benzo[a]pyrene by conversion to water-soluble metabolites has also been reported (Nowak et al., 1988).

Glutathione *S*-transferases (GST) are multifunctional proteins that catalyze

TABLE H-3 Examples of Interactions Between Inherited Cancer Predisposition and Environmental Carcinogens

Candidate Gene	Condition	Examples of Cancer Site	Environmental Carcinogens	Odds Ratio (95% confidence interval)	Reference
XPAC	Xeroderma pigmentosum	Skin	Sunlight	>1,500	Cleaver, 1968
Unknown	Epidermodysplasia verruciformis	Skin	Sunlight and human papillomavirus	(#30% of affected people)	Orth, 1986
CYP2D6	Extensive-hydroxylator phenotype	Lung	Tobacco smoke; Asbestos; PAH[a]	6.1(2.2-17.1); 18.4 (4.6-74); 35.3 (3.9-317)	Caporaso et al., 1990 Caporaso et al., 1989 Caporaso et al., 1989
YP1A1	Extensive-metabolic phenotype[b]	Lung	Tobacco smoke	7.3 (2.1-25.1)	Nokachi et al., 1991
Ha-ras	Restriction-fragment length polymorphisms (rare alleles)	Lung[c]	Tobacco smoke	4.2(1.1-16)	Sugimura et al., 1990
NAT2	Slow-acetylator phenotype (recessive inheritance)	Bladder	Aromatic amine dyes	16.7 (2.2-129)	Cartwright et al., 198
NAT2	Rapid-acetylator phenotype (dominant inheritance)	Colon	Unknown	1.4 (0.6-3.6); 4.1 (1.7-10.3)	Lang et al., 1986 Ilett et al., 1987
CYP1A1 GSTI	Metabolic balance between activation and detoxification	Lung[d]	Aromatic hydrocarbons	9.1(3.4-24.4)	Hayashi et al., 1992 Seidegard et al., 1986 Hayashi et al., 1992
GSTI	Metabolic balance between activation and detoxification	Lung[e]	Aromatic hydrocarbons	3.5(1.1-10.8)	Seidegard et al., 1986

[a] Polycyclic aromatic hydrocarbon.
[b] Increased prevalence in Japanese.
[c] Nonadenocarcinoma lung cancer in African-Americans.
[d] Squamous cell carcinoma in Japanese.
[e] Adenocarcinoma.

the conjugation of glutathione to electrophiles, including the ultimate carcinogenic metabolite of benzo[a]pyrene, and are considered to be one means of detoxifying carcinogenic PAHs. The three isoenzymes of GST (α- , μ, and π) vary in their substrate specificity, tissue distribution, and activities among individuals. Expression of GST-μ is inherited as an autosomal dominant trait, and people with low GST-μ activity might be at greater risk of lung cancer caused by cigarette-smoking (Seidegard et al., 1986, 1990). In addition, an interaction between GST-μ and CYP1A1 genotypes has been observed (Hayashi et al., 1992). People with a homozygous deficient GST-μ genotype and a CYP1A1 genetic polymorphism in the heme-binding region of this cytochrome P450 enzyme have an increased risk of squamous cell carcinoma of the lung (odds ratio, 9.07; 95% confidence interval, 3.38-24.4) and adenocarcinoma of the lung (odds ratio, 3.45; 95% confidence interval, 1.10-10.8).

DAN-Adduct Formation

DNA adducts are one form of genetic damage caused by chemical carcinogens and might lead to mutations that activate proto-oncogenes and inactivate tumor-suppressor genes in replicating cells. The steady-state concentrations of the adducts depend on both the amount of ultimate carcinogen available to bind and the rate of removal from DNA by enzymatic repair processes. The genomic distributions of adduct formation and repair are nonrandom and are influenced by both DNA sequence and chromatin structure, including protein-DNA interactions that prevent electrophilic attack of the DNA by the active form of the carcinogen.

Although the major DNA adducts are qualitatively similar for the chemical carcinogens so far studied in the in vitro models, quantitative differences have been found among people and among various tissue types. The differences due to interindividual variation and intertissue variation within an individual in formation of DNA adducts have a range of a factor of about 10-150 among humans. The interindividual distribution is generally unimodal (i.e., a curve with a single peak), and the variation is similar in magnitude to that found in pharmacogenetic studies of drug metabolism (Harris, 1989).

DNA-Repair Rates

DNA-repair enzymes modify DNA damage caused by carcinogens in reactions that generally result in the removal of DNA adducts. Studies of cells from donors with xeroderma pigmentosum have been particularly important in expanding understanding of DNA excision repair and its possible relationship to risk of cancer. The rate, but not the fidelity, of DNA repair can be determined by measuring unscheduled DNA synthesis and removal of DNA adducts; substantial interindividual variation in DNA repair rates has been observed (Setlow, 1983). The fidelity of DNA repair could also vary among people, and recent

advances in the identification of mammalian DNA-repair genes and their molecular mechanisms should soon provide an opportunity to investigate the fidelity of repair by excision. In addition to severe decreases in excision-repair rates in the cells of individuals with the recessive genetic conditions xeroderma pigmentosum cells, an approximately 5-fold variation among people in unscheduled DNA synthesis induced by UV exposure of lymphocytes in vitro has been found in the general population (Setlow, 1983). DNA repair might involve tens of enzymes and cofactors, and genetic polymorphisms of the genes encoding these repair enzymes could be responsible for the variation among both persons and groups.

Interindividual variation has been noted in the activity of O^6-alkyldeoxyguanine-DNA alkyltransferase; this enzyme repairs alkylation damage to O^6-deoxyguanine. Wide variations (a factor of about 40) in this DNA-repair activity have been observed between persons in different types of tissues (Grafstrom et al., 1984; D'Ambrosio et al., 1984, 1987), and fetal tissues exhibit only about 20-50% as much activity as the corresponding adult tissues (Myrnes et al., 1983).

A unimodal distribution of repair rates of benzo[a]pyrene diolepoxide-DNA adducts has been observed in human lymphocytes in vitro (Oesch et al., 1987). The interindividual variation was substantially greater than the intraindividual variation, and this suggests a role of inherited factors. The influence of those variations in DNA-repair rates in determining tissue site and risk of cancer in the general population remains to be determined.

Synergistic Effects Of Carcinogens

People who have been exposed to one type of carcinogen might be at increased risk of cancer when exposed, simultaneously or in sequence, to another type (Table H-4). Cigarette smokers, already at greater risk of lung cancer than nonsmokers, are at even greater risk if they are occupationally exposed to asbestos (Selikoff and Hammond, 1975; Saracci, 1977) or radon (Archer, 1985). Recently, a synergistic effect between hepatitis B virus and aflatoxin B_1 in the risk of hepatocellular carcinoma has been described (Ross et al., 1992).

Age

Children exposed to carcinogens might be at higher risk of cancer than adults (NRC, 1993; ILSI, 1992). Studies of atomic-bomb survivors and persons irradiated for the treatment of cancer have found the risk of future cancers of breast, lung, stomach, thyroid, and connective tissues to be greater when exposure is at lower ages (Fry, 1989). On the other hand, the elderly may be at increased susceptibility to other carcinogenic stimuli, cue to diminished immune surveillance, exposure to multiple drugs, or simply to a larger accumulation of DNA damage that places some cells at high risk of initiation from one more "hit" to the genetic material.

TABLE H-4 Examples of Synergistic Effects Among Chemical, Physical, and Viral Carcinogens.

Cancer Type	Carcinogens	Odds Ratio (95% Confidence Interval)	Reference
Liver	Hepatitis B virus; + aflatoxin B_1 exposure	4.8 (1.2-19.7) 60 (6.4-561.8)	Ross et al., 1992
Esophagus	Tobacco smoke; + alcoholic beverages	5.1 (-); 44.4 (-)	Tuyns et al., 1977
Mouth	Tobacco smoke; + alcoholic beverages	2.4 (-); 15.5 (-)	Rothman and Keller, 1972
Lung	Tobacco smoke; + occupational; asbestos exposure	8.1 (5.2-12.0) 92.3 (59.2-137.4)	Selikoff and Hammond, 1975 Saracci, 1977

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Appendix I

This appendix is split into three parts. The first discusses aggregate risk of occurrence of one or more nonthreshold, quantal, toxic end points caused by exposure to multiple agents (assuming independent actions). The second is a summary assessment of independence in interanimal tumor-type occurrence in the NTP rodent-bioassay database. The third discusses methods for aggregating uncertainty and interindividual variability in predicted risk.

Appendix I-1

Aggregate Risk of Nonthreshold, Quantal, Toxic End Points Caused by Exposure to Multiple Agents (Assuming Independent Actions)

The aggregate increased probability P of occurrence of any of n (presumed) nonthreshold end points caused by exposure to an environmental mixture of m toxic agents may be conveniently expressed under a few general assumptions. First, assume that the m agents are present in an environmental mixture at corresponding concentrations C_i, where $i = 1,2,\ldots,m$, each of which produce, in exposed people, corresponding lifetime, time-weighted average biologically effective dose rates D_{ij}, each causing one or more of n quantal (all or none) toxic end points T_j, where $j = 1,2,\ldots,n$ (see Figure I-1). Let O_{ij} denote the occurrence of a particular jth end point T_j induced by effective dose rate D_{ij}, and assume that T_j has a background occurrence probability of $p_j = \text{Prob}(O_{ij} \mid D=0)$ for total effective dose D due to all relevant agents and that O_{ij} may arise only by events independent of those giving rise to either the background incidence rate of T_j or to events O_{gh} for any g and h such that $g \neq i$, $1 \leqq g \leqq m$, $h \neq j$, and $1 \leqq h \leqq n$. Finally, for very small values of D_{ij}, assume that the corresponding increased probability of occurrence of the T_j is defined by an independent "one-hit" (nonthreshold, low-dose linear) function of D_{ij}. In the following, $\cap$, $\cup$, and the overbar denote the logical union, intersection, and negation operations, respectively.

It follows from the stated assumptions and definitions that a D_{ij}-induced increased probability P_{ij} of T_j occurrence, conditional on its independent background rate p_j, is:

(1)

$$P_{ij} = \text{Prob}(O_{ij}) = \frac{\text{Prob}(T_j \mid D = D_{ij}) - p_j)}{1 - p_j},$$

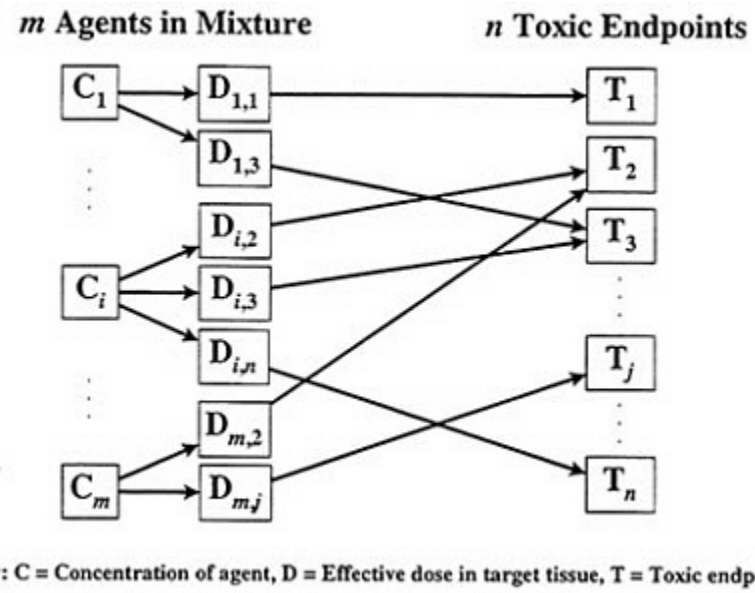

FIGURE I-1 Multiple agents associated with multiple toxic end points.

in which q_{ij} (the linear coefficient in dose) is the parameter characterizing the "potency" (or low-dose increased occurrence probability per unit dose) of compound i for inducing end point T_j. Under the stated assumptions, $P_{ij}=q_{ij}=0$ for any j^{th} end point T_j that is unaffected by D_{ij} alone, regardless of concurrent doses from any other agents. The quantity of interest—aggregate increased probability P of occurrence of any of the n end points caused by any of the m toxic agents—may therefore be expressed as

$$P = \text{Prob}\left(O_{1,1} \cup O_{1,2} \cup \ldots \cup O_{1,n} \cup O_{2,1} \cup \ldots \cup O_{m,1} \cup \ldots \cup O_{m,n}\right), \qquad (2)$$

which, by de Morgan's rule, may be rewritten as

$$P = \text{Prob}\left(\overline{O}_{1,1} \cap \overline{O}_{1,2} \cap \ldots \cap \overline{O}_{1,n} \cap \overline{O}_{2,1} \cap \ldots \cap \overline{O}_{m,1} \cap \ldots \cap \overline{O}_{m,n}\right), \qquad (3)$$

from which, by Equation 1 and the independence assumption, it follows that

$$P = 1 - \prod_{i=1}^{m}\prod_{j=1}^{n}\left(1 - P_{ij}\right), \qquad (4)$$

$$P = 1 - \exp\left(-\sum_{i=1}^{m}\sum_{j=1}^{n} q_{ij} D_{ij}\right). \qquad (5)$$

For very small values of P ($\ll 1$) relevant to environmental regulatory concern, P is well approximated by

$$P \approx \sum_{i=1}^{m} \sum_{j=1}^{n} q_{ij} D_{ij} \,. \qquad (6)$$

If no information is available concerning target-tissue-specific pharmacokinetics, D_{ij} is sometimes taken to be either the absorbed dose rate (e.g., milligrams of agent *i* absorbed per kilogram of body weight per day) or a whole-body surrogate for effective dose (e.g., estimated milligrams of agent *i* metabolized per kilogram of body weight per day), that is, a measure of dose identical for all of the particular toxic end point(s) considered. In this case, $D_{ij}=D_i$ is independent of *j* for any given i^{th} agent, such that Equation 6 may be rewritten as

$$P \approx \sum_{i=1}^{m} Q_i D_i \,, \qquad (7)$$

in which Q_i is the sum of q_{ij} for *j* ranging from 1 to *n* and represents the aggregate potency of agent *i* for inducing at least one of the *n* end points considered.

When applying relations like those represented by Equations 5-7, *q, Q, D*, and hence *P* may represent quantities subject to uncertainty or interindividual variability characterized by different probability distributions. If distributed variates are involved, a meaningful confidence bound on *P* cannot generally be obtained by performing the indicated summations with the same bound on all values of *q, Q*, and *D*. In the special case that, say, Q_i and D_i in Equation 7 are all independent and *m* is sufficiently large, the estimate of *P* will tend to be normally distributed; however, asymptotic normality is not likely to be useful in situations involving relatively small *m* and *n*. If a statistical upper confidence bound is desired is desired for *P*, Monte Carlo procedures will therefore generally be needed.

Appendix I-2

Independence in Inter-Animal Tumor-Type Occurrence in the NTP Rodent-Bioassay Database

Animal cancer bioassay data have been used as the basis for estimating carcinogenic potency (i.e., increased risk per unit dose at very low doses) of a chemical to which a human of average cancer susceptibility might be exposed over a lifetime (Anderson et al., 1983; EPA, 1986, 1992). The bioassay data available may indicate that multiple tumor types are induced in exposed bioassay animals. In this case, it is generally desired to estimate the aggregate cancer potency exhibited by the compound in the bioassay animals, that is, the effectiveness in the experimental animals of the compound in eliciting any one or more of the elevated tumor types. The estimated aggregate cancer potency in bioassay animals may then be used to extrapolate a corresponding potency of that compound in a human of average susceptibility (EPA, 1986, 1992). Neither this interspecies extrapolation nor the issue of human interindividual variability in cancer susceptibility (discussed in Chapter 10) are the subject of this appendix (I-2). Rather, this appendix focuses on the extent of tumor-type correlations in bioassay animals, which in turn bears on the question of how properly to estimate the aggregate cancer potency of a compound exhibited in bioassay animals for a compound that induces multiple tumor types.

One approach to estimating aggregate cancer potency in bioassay animals has been to apply a dose-response model to tumor-incidence rates with the numerators defined as the number of animals with one or more of the histologically distinct and significantly elevated tumor types (EPA, 1986). By this procedure, either a control or a dosed animal with multiple tumor types counts the same as an animal with only a single tumor type. If the tumor types occur in a statistically independent fashion among the bioassay animals tested, it follows that this procedure may under- or over-estimate true aggregate potency because it has the

effect of randomly excluding tumor-response information concerning both control and dosed animals (Bogen, 1990).

If potency is estimated using a multistage model (which is in effect a one-hit model at very low doses), and if tumor types assort independently among the animals tested, the statistical problem raised by EPA's tumor-pooling approach is avoided completely if aggregate potency is instead estimated as the sum of tumor-type-specific (that is, independent-end-point-specific) potencies (see Appendix I-1). This alternative to EPA's procedure, however, depends on the validity of the independence assumption regarding tumor-type occurrence within bioassay animals, which is the subject of this appendix (I-2).

In some of the few studies that have focused on tumor-type associations within individual animals, a few significant associations have been noted, mostly negative associations involving one or two specific tumor types among associated pairs. Significant ($p \ll 0.05$) ageand treatment-adjusted associations for five of 21 sex-specific pairs from six tumor types investigated were reported by Breslow et al. (1974) for experiments involving over 4000 CF-1 mice exposed to DDT, urethane or nothing: negative associations between lymphomas and each of hepatomas (males), lung adenomas (males and females), and mammary and ovarian tumors (females), and a positive association between lymphomas and bone tumors (males). (Upon adjustment for multiple significance tests (Wright, 1992), the association between lymphomas and mammary tumors observed in that study may not be significant at the 0.05 level.) Breslow et al. (1974) suggested that the negative lymphoma-related associations, except perhaps those involving liver tumors, were all likely to be spurious, "due to the relative rapidity with which lymphomas tend to kill their bearers." A significant negative association between lymphomas and liver tumors (but not lung tumors) in 1478 similarly exposed CF-1 mice was later confirmed, even after accounting for the relatively rapid lymphoma lethality by use of serial sacrifice information (Wahrendorf, 1983). A significant negative correlation between malignant lymphoma and proliferative hepatocellular lesions at death/sacrifice was also found among 1858 male ICI mice (Young and Gries, 1984). Haseman (1983) also noted this significant negative correlation in raw tumor-incidence data for F344 rats from 25 National Toxicology Program (NTP) bioassays (not analyzed at the level of individual animals).

The most comprehensive study of this type, involving an examination of age- and treatment-adjusted associations between (66 possible) pairs of 12 tumor types at death/sacrifice in 3813 gamma-irradiated female BALB/c mice, reported 21 significant ($p \ll 0.05$) positive or negative associations, 10 of which were negative and involved reticular tumors considered to be rapidly lethal and generally also involved other tumors considered to be lethal in the animals studied; most of these 10 associations were considered to be spurious due to the effect of lethality (Storer, 1982). The remaining associations considered significant generally were positive and involved endocrine-related tumors (Harderian, mammary, adrenal,

and pituitary tumors), and none of these involved liver tumors. Aside from associations involving reticular sarcomas, and after appropriate statistical adjustment for multiple tests of significance (Wright, 1992), only three of 55 remaining possible associations reported by Storer (1982) appear to be significant at a 0.05 level, all involving Harderian-gland tumors, which, along with ovary, adrenal and pituitary tumors, were all considered to be nonlethal in the animals studied. A recent study of liver-tumor and reticulum-cell-sarcoma incidence in 1004 gamma-irradiated female C3H mice supported a significant negative correlation of these tumor types, even after adjustment for the relative lethality of the reticular tumors using cause-of-death information available in that study (Mitchell and Turnbull, 1990).

In other smaller studies, an assumption of independence in tumor-types at death/sacrifice was shown to be consistent with ED01 data on four different tumor types in 366 control female BALB/c mice and six tumor types elevated in 193 such mice exposed to 2-acetylaminofluorine (Finkelstein and Schoenfeld, 1989), as well as with Hazelton Laboratory data on three different tumor types elevated in a total of 142 male albino rats exposed to dibromochloropropane (Bogen, 1990).

No comprehensive study of animal-specific tumor-type occurrences at death/sacrifice has been conducted using the extensive set of available NTP rodent-bioassay data, on which most cancer-potency assessment for environmental chemicals is currently based. This report presents the results of such an analysis (Bogen and Seilkop, 1993) conducted on behalf of the National Research Council's Committee on Risk Assessment for Hazardous Air Pollutants.

Data Description

Tumor-Type associations among individual animals were examined for both control and treated animals using pathology data from 62 B6C3F1 mouse studies and 61 F/344N rat studies obtained from a readily available subset of the NTP carcinogenesis bioassay database. Most studies were 2-year studies, although a few were shorter (e.g., 15 months). Separate analyses were conducted for the four sex/species combinations (male and female mice, male and female rats) corresponding to the compounds and species indicated in Table I-1. Analysis was confined to the following common tumor types (occurring at a rate >5%):

Rats:	Adrenal gland:	medulla pheochromocytomas (benign or malignant)
	Thyroid gland:	C-cell adenomas or carcinomas
	Pituitary gland:	carcinomas or adenomas
	Mammary gland:	fibromas, fibroadenomas, carcinomas, or adenomas
	Leukemia:	lymphocytic, monocytic, mononuclear, or undifferentiated.

Mice:	Lung:	alveolar/bronchiolar adenomas or carcinomas
	Liver:	hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas
	Lymphoma:	histiocytic, lymphocytic, mixed, NOS, or undifferentiated.

TABLE I-1 NTP Studies from Which Data Were Used

CHEMICAL	MICE[a]	RATS[a]
O-Chlorobenzalmalononitrile (CS-2)		X
1,2,3-Trichloropropane	X[b]	X[c]
1,3-Butadiene (butadiene)	X	
2,4-Diaminophenol Dihydrochloride	X	X
2,4-Dichlorophenol	X	X
3,3'-Diemthoxybenzidine Dihydrochloride		X[c,d]
3,3'-Dimethylbenzidine Dihydrochloride		X[c,d]
4,4-Diamino-d,d-Stilbenedisulfonic Acid	X	X
4-Hydroxyacetanilide	X	X
4-Vinyl-1-cyclohexene Diepoxide	X	X
Allyl glycidyl ether	X	
Benzaldehyde	X	X
Benzyl Acetate	X	X
Bromoform	X	X
γ-Butyrolactone	X	X
C.I. Acid Red 114		X[c,d]
C.I. Direct Blue 15		X[c,d]
Carvone	X	
Chloramine	X	X
Chloroacetophenone	X	X
p-Chloroaniline	X	X
p-Chlorobenzalmalononitrile (CS-2)	X	
C.I. Pigment Red 23	X	X
C.I. Pigment Red 3	X	X
Coumarin	X	X
DL-Amphetamine sulfate	X	X
Dichlorvos	X	X
Dihydrocoumarin	X	X
Dimethoxane	X	X
Diphenylhydantoin	X	X
Ephinephrine HCl	X	X
Ethyl chloride	X	X
Ethylene glycol	X	
Ethylenethiourea	X	X
Firemaster FF-1 Polybrominated Biphenyl	X	X
Furan	X[e]	X
Furfural	X	X
HC Yellow 4	X	X

CHEMICAL	MICE[a]	RATS[a]
Hexachloroethane		X
Hydroquinone	X	X
Managanese sulfate	X	X
Mercuric chloride	X	X
Methyl bromide	X	
Monochloraoacetic acid	X	X
N-Methylolacrylamide	X[b]	X
Naphthalene	X	
p-Nitroaniline	X	
Nitrofurantoin	X	X
o-Chlorobenzalmalononitrile (CS-2)	X	
o-Nitroanisole	X	X
Ochratoxin A		X
p-Nitroaniline	X	
Pentachloroanisole	X	X
Pentachlorophenol, Dowicide CD-7	X[e]	
Pentachlorophenol, Technical grade	X	
Pentaerythritol Tetranitrate	X	X
Phenylbutazone	X	X
Polysorbate 80	X	X
Probenecid	X	X
Quercetin		X
Resorcinol	X	X
Rhodamine 6G	X	X
Roxarsone	X	X
Sodium Azide		X
Sodium Fluoride	X	X
Succinic Anhydride		X
Talc	X	
Tetranitromethane	X	X
Titanocene dichloride		X
Toluene	X	X
Triamterene	X	X
Tris(2-chloroethyl) phosphate	X	X
Vinyl toluene	X	X

[a] NTP studies from which treated-animal data, in addition to control-animal data, were taken for use in this analysis are indicated by a superscript.

[b] Liver and Harderian-gland effects in treated animals.

[c] Zymbal-gland and clitoral or preputial-gland effects in treated animals.

[d] Liver and skin effects in treated animals.

[e] Liver and adrenal-gland effects in treated animals.

Source: Bogen and Seilkop, 1993.

Analyses of correlations between tumor occurrence in treated animals were based on subsets of the control-animal data, comprising studies for which the NTP declared "clear evidence" of an effect at multiple sites and for which pairs of such effects were exhibited in more than one study (resulting in the use of five rat studies and four mouse studies). The treated animal studies involved tumor types that differed from the control-animal studies, namely, adenomas or carcinomas of: liver, Zymbal's gland, clitoral /preputial gland, and skin in rats; and liver, adrenal and Harderian gland in mice. In both controland treated-animal analyses, evidence of associations from individual studies were pooled as described below.

Statistical Methods

Associations among statistically significantly elevated tumor-types within individual animals may pertain either to tumor onset probabilities or to prevalence at death/sacrifice or to both. It is well known that associations present at death/sacrifice may differ, sometimes substantially, from those relating to tumor onset, and that the former may be heavily influenced by the latter as a result of the time-dependent action of competing risks (Hoel and Walburg, 1972; Breslow et al., 1974; Wahrendorf, 1983; Lagakos and Ryan, 1985). For example, if the onset probabilities of two different tumor types are statistically independent, but in addition both are rapidly lethal, then there is little probability of their joint occurrence within an individual animal and thus their prevalence at death/sacrifice will be negatively correlated. This fact was the basis for concluding probable "spurious" negative correlations involving rapidly lethal tumor types in previous assessments of tumor-type associations in rodents (Breslow et al., 1974; Storer, 1972).

Unambiguous detection of associations in onsets of different tumor types requires either serial-sacrifice information or animal- and tumor-specific lethality information (Hoel and Walburg, 1972; Wahrendorf, 1983; Lagakos and Ryan, 1985; Mitchell and Turnbull, 1990), neither of which is available for the NTP data analyzed here. Thus, the present analysis was primarily restricted to an assessment of age-adjusted correlations in tumor-types present at death/sacrifice. This approach provides definitive information on onset (as well as terminal prevalence) correlations only if all tumor types are incidental to fatality. However, as described below, a crude assessment of onset-probability correlations was also conducted using information on tumor lethality obtained from the data studied.

Evaluation of the correlations between occurrences between pairs of tumor types in individual animals observed at death/sacrifice was based on age-adjustment of information from 24 previous similar studies (Breslow et al., 1974; Storer, 1982; Young and Gries, 1984; Finkelstein and Schoenfeld, 1989). Five survival-age strata within each study were used: (1) first 365 days, (2) 366-546 days (1.5 years), (3) 547-644 days (~1.75 years), (4) 644-terminal sacrifice (~2

years), (5) terminal sacrifice. Further stratification addressed the inclusion of the highest two dose groups. Thus, the potential number of analytical strata (i.e., 24 times 2 (the number of dose levels). The method of Mantel and Haenszel (1959) was used to combine results from stratum-specific contingency tables and to assess two-tailed significance of overall associations between tumor occurrences. Overall correlations are represented as the weighted averages of corresponding stratum-specific measures, using the numbers of animals in the strata as weights. Adjusted p-values accounting for multiple tests of a zero-correlation null hypothesis were obtained for all control and all treated rats and mice using Hommel's modified Bonferroni procedure (Wright, 1992).

In the absence of serial sacrifice or lethality information, associations between onsets of pairs of tumor types in individual NTP-bioassay animals were evaluated using two crude techniques. First, a separate correlation analysis was undertaken as above, but using only terminal sacrifice data. This approach provides definitive information on onset (as well as terminal prevalence) correlations only if no animals die prior to terminal sacrifice, but may nevertheless provide meaningful information if a sufficiently large fraction of animals survive until sacrifice. The second approach used was the three-by-three contingencytable method for detection of disease-onset associations devised by Mitchell and Turnbull (1990), which requires lethality determinations for each tumor occurrence in each animal. When in doubt regarding such lethality, Mitchell and Turnbull (1990) recommend that it would be prudent to classify a particular occurrence as lethal, because while doing so falsely may reduce the power of the test, the null distribution will not be affected. Thus, the Mitchell-Turnbull test was applied under the assumption that all occurrences of a given tumor type were lethal for all plausibly lethal tumor types. Tumor-Type lethality was investigated using Mann-Whitney U statistics comparing survival times of tumor-bearing and tumor-free animals, where all study-specific results for a given control or treated species and sex were combined to form an overall test by summing these U statistics and dividing this sum by the square root of the sum of the corresponding variances.

Results And Discussion

The results of our analysis of correlations in incidence at death/sacrifice of tumor types in control rats and mice are summarized in Table I-2. These results indicate four significant ($p^* < 0.05$) but small correlations among 20 sex/tumor-type-pairs investigated in rats (pituitary vs. leukemia in both sexes, and mammary vs. leukemia or pituitary in females—where all those involving leukemia were negative), and no similarly significant correlations among 12 sex/tumor-type-pairs investigated in mice. Corresponding results for treated rats and mice are summarized in Table I-3. Significant ($p^* < 0.05$) but again generally quite small correlations appear present for two of 12 sex/tumor-type-pairs investigated

TABLE I-2 Correlations Between Tumor Prevalence at Death/Sacrifice in Control Groups

SPECIES Tumor Types	Sex	Corr.	n	p-value	Adjusted p*-value
RATS					
Adrenal × Leukemia	Females	0.060	2794	0.017	0.272
	Males	0.025	2786	0.257	1
Adrenal ×	Females	0.041	2692	0.138	1
Thyroid	Males	-0.024	2593	0.342	1
Thyroid × Leukemia	Fernales	-0.032	2942	0.120	1
	Males	-0.045	2827	0.076	1
Pituitary × Leukemia	Females	-0.158	3057	C0.001	<0.020
	Males	-0.080	2990	<0.001	<0.020
Mammary × Leukemia	Females	-0.074	3088	<00.001	<0.020
	Males	-0.025	3045	<0.001	1
Mammary × Pituitary	Females	0.076	3057	<0.001	<0.020
	Males	0.027	2990	0.301	1
Pituitary × Thyroid	Females	-0.002	2916	0.982	1
	Males	0.026	2784	0.254	1
Pituitary × Adrenal	Females	-0.029	2770	0.268	1
	Males	-0.010	2739	0.659	1
Mammary × Adrenal	Females	-0.015	2794	0.597	1
	Males	0.008	2786	0.835	1
Mammary × Thyroid	Females	-0.011	2942	0.642	1
	Males	0.008	2827	0.846	1
MICE					
Liver × Lung	Females	-0.003	3058	0.978	0.204
	Males	-0.022	3011	0.322	1
Liver × Lymphoma	Females	-0.029	3059	0.185	1
	Males	-0.053	3014	0.017	0.204
Lung × Lymphoma	Females	-0.054	3071	0.018	0.204
	Males	-0.008	3016	0.791	1
Pituitary × Lung	Females	0.014	2898	0.592	1
	Males	0.025	2725	0.879	1
Pituitary × Liver	Females	0.020	2891	0.393	1
	Males;	-0.074	2724	0.307	1
Pituitary × Lymphoma	Females	-0.041	2899	0.058	0.580
	Males	0.011	2727	0.806	1

Source: Bogen and Seilkop, 1993.

TABLE I-3 Correlations Between Tumor Prevalence at Death/Sacrifice in Chemically Affected Groups

SPECIES Tumor Types	Sex	Corr.	n	p-value	Adjusted p˜value
RATS					
Liver × Zymbal's Gland	Females	0.005	498	0.927	0.961
	Males	0.004	499	0.961	0.961
Zymbal's Gland × Clitoral/	Females	-0.117	590	0.012	0.12
Preputial Gland	Males	-0.152	577	0.003	0.033
Skin × Zymbal's Gland	Females	-0.065	500	0.272	0.961
	Males	-0.071	500	0.213	0.961
Liver × Skin	Females	0.041	498	0.630	1
	Males	0.172	498	0.002	0.24
Liver × Clitoral/Preputial	Females	0.034	488	0.658	1
Gland	Males	-0.078	487	0.187	1
Skin × Clitoral/Preputial	Females	0.023	489	0.762	1
Gland	Males	0.027	487	0.735	1
MICE					
Liver × Adrenal Gland	Females	0.153	194	0.245	0.49
	Males	0.257	196	0.076	0.228
Liver × Harderian Gland	Females	0.236	190	0.004	0.016
	Males	0.024	191	0.889	0.889

Source: Bogen and Seilkop, 1993.

in treated rats (Zymbal's vs.preputial gland and liver vs. skin tumors in males) and for one of four sex/tumor-type-pairs investigated in treated mice (liver vs. Harderian gland in females), where the liver-related correlations were both positive.

Terminal-sacrifice animals represented 66 to 68% of all the control mice and 53 to 63% of all control rats referred to in Table I-2. Analysis of tumor-type-prevalence correlations in only these animals revealed only a single significant ($p^* < 0.05$) correlation, that between mammary and pituitary tumors in female rats ($r=0.080$, $p^*=0.013$). Thus, the latter positive (albeit quite small) correlation may pertain to onset as well as prevalence-at-death/sacrifice correlations,

whereas the negative leukemia-related correlations noted above for all control rats did not persist in terminal-sacrifice animals. This finding could be explained by relative lethality associated with rodent leukemia/lymphoma, which has been noted in previous studies (Breslow et al., 1974; Wahrendorf, 1983; Young and Gries, 1984; Portier et al., 1986). Terminal-sacrifice animals represented only 14 to 16% of all the treated rats and 20 to 55% of all treated mice referred to in Table I-3. Correlation analyses for these treated animals yielded no significant ($p^* < 0.05$) correlations, which sheds less light on tumor-onset associations given the greater non-representativeness of these animals.

Our examination of differences in survival time in animals with particular tumors vs. tumor-free animals revealed a few significant differences in control and treated rats. Leukemia in both sexes of control F344 rats studied was associated with a significant reduction in mean survival time ($p<0.001$). However, this reduction was rather modest: 75% of leukemia -bearing animals lived until the 23rd month of the studies and 50% lived until terminal sacrifice. In contrast, 75% of the leukemia-free animals survived until terminal sacrifice. Thus, any effect of leukemia lethality in inducing negative correlations with other cancers is likely to be small.

There was also evidence that Zymbal's gland tumors in treated rats resulted in reduced survival times (males, $p<0.001$; females, $p=0.003$), where the median survival times were reduced by about four months in males (546 vs. 427 days—reduction for more striking than that for leukemia in control males) and by about one month in females. When leukemia and Zymbal's gland tumors in animals dying before terminal sacrifice were assumed to be lethal and all other tumor types incidental, the Mitchell-Turnbull test yielded similar results to those obtained using the unmodified age-stratified analysis. In particular, it provided strong evidence that the small, negative associations between leukemia and pituitary-gland tumors in control rats were not due to chance or to differential lethality (males, $p<10\text{-}9$; females, $p=0.000057$), and it indicated the same regarding the small, negative associations between Zymbal's-gland tumors and preputial-/clitoral-gland tumors in treated rats ((males, $p=0.009$; females, $p=0.002$).

In summary, no evidence was found for any large correlation in either the onset probability or the prevalence-at-death/sacrifice of any tumor-type pair investigated in control and treated rats and mice, although a few of the small correlations present were statistically significant. This finding must be qualified to the extent that tumor-type onset correlations were measured indirectly given the limited nature of the data analyzed. Taken together, these findings indicate that tumor-type occurrences in B6C3F1 mice and F344 rats used in the NTP bioassays analyzed were in most cases nearly independent, and that departures from independence, where they did occur, were small.

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Appendix I-3

Aggregation of Uncertainty and Variability

This appendix illustrates why a distinction between uncertainty and interindividual variability within input variates must be maintained, if a quantitative characterization of uncertainty in population risk or in individual risk is sought. Two types of mathematical model used to predict risk are considered here for an exposed population of size n. The first model is a simple one in which a predicted low level of exposure-related increased risk R is well approximated by the product of U (a purely uncertain variate) and V (a purely heterogeneous variate that models interindividual variability).

$$\begin{aligned} R &= 1 - \exp\{-(U_1\, U_2\, U_3)\,(V_1\, V_2\, V_3)\} \\ &\approx (U_1\, U_2\, U_3)\,(V_1\, V_2\, V_3) \text{ for } R \ll 1, \\ &\approx UV \text{ for } R \ll 1, \end{aligned} \qquad (1)$$

where U_i and V_i represent uncertain and heterogeneous variates, respectively, for i= 1,2,3. That is, for a given value of i, V_i models the set of n particular (known or assumed) quantities pertaining to n individuals in the population at risk, whereas U_i models (in this case, using a single, uncertain multiplicative factor) the uncertainty associated with each one of those n quantities; this type of distinction is explained further by Bogen and Spear (1987) and Bogen (1990). In the present simple model, for example, U_1 and V_1 might refer to lifetime time-weighted average exposure, U_2 and V_2 to biologically effective dose per unit exposure, and U_3 and V_3 to cancer "potency" (increased cancer risk per unit biologically effective dose as dose approaches zero). In this case, V_3 would model interindividual variability in susceptibility to dose-induced cancer.

A more complicated risk model assumes that risk R equals some more general function $\boldsymbol{H}(\mathbf{U},\mathbf{V})$ of the vectors $\mathbf{U}$ and $\mathbf{V}$ of purely uncertain and purely heterogeneous variates, respectively. In the following discussion, an overbar denotes the expectation operation with respect to all heterogeneous variates ($\mathbf{V}$) associated with the overbarred quantity and angle-brackets, <>, shall denote the expectation operation with respect to all uncertain variates ($\mathbf{U}$) associated with the bracketed quantity (that is, $\bar{R} = E_V(R)$ and $\langle R \rangle = E_U(R)$, where E is the expectation operator). Also, $F_X(x)$ shall denote the cumulative probability that $X \leqq x$, for some particular value x of any given variate X.

Population Risk

Population risk, N, is the number of additional cases associated with predicted risk R. By definition, N is an uncertain variate, not a heterogeneous one. Uncertainty in N, however, is often ignored under the assumption that it is necessarily small in relation to the expected value of N for large n. For example, in its recent radionuclide-NESHAPS uncertainty analysis, EPA (1989, p. 7-6) stated that

> Because population risks represent the sum of individual risks, uncertainties in the individual risks tend to cancel each other out during the summing process. As a result, the uncertainty in estimates of population risk is smaller than the uncertainty in the estimates of the risks associated with the individual members of the population. Because of this, [our] uncertainty analysis is limited to the uncertainty in risks to an individual.

This assumption is clearly false, as is demonstrated by a comparison of the case (a) of n identical but extremely uncertain individual risks with the case (b) of n identical individual risks all equal to the known constant (i.e., completely certain value) r, for large n. Uncertainty in population risk in case (a) must remain extremely large independent of n, whereas in case (b) the cumulative probability distribution function (cdf) for the ratio N/n is simply a normalized binomial distribution that has smaller and smaller variances around the true value r as $n \rightarrow \infty$. The key point is that in the relationship between n uncertain individual risks and the corresponding uncertain population risk, many of the *uncertain* characteristics of each of the individual risks are not independent, but rather reflect quantities such as potency-parameter estimation error or model-specification error that pertain *identically* or in much the same way to *all* individuals at risk, and thus do not in any sense "cancel out" upon summation.

The uncertain magnitude of population risk N (i.e., the predicted number of cases) is well approximated for large n by the uncertainty quantity $n\ \bar{R}$ where for the simple risk model $\bar{R} = \mathbf{U}\bar{\mathbf{V}}$ and for the more complicated risk model $\bar{R} \approx \mathbf{H}(\mathbf{U},\bar{\mathbf{V}})$ as a first-order approximation (Bogen and Spear, 1987). For large n and $0 \leqq j \leqq n$, $F_N(j)$ is generally well approximated by the expected Poisson probability for the compound-Poisson variate with uncertain parameter $n\ \bar{R}$; for example

$F_N(0) = \int 1/0 e^{-nr} d F_{\bar{R}}(r)$ (Bogen and Spear, 1987). The expected value, $\langle N \rangle = n\langle \bar{R} \rangle$, of risk has traditionally has been used in defining risk-acceptability criteria addressing *N*; however, criteria intended to be conservative with respect to uncertainty associated with *N* ought logically to refer to some upper confidence bound on *N*, rather than to its expected value.

Individual Risk

Predicted risk *R*, as defined above, is a variate that clearly may reflect both uncertainty and interindividual variability. It is tempting to assume that predicted risk to a given individual—say, the person with the j^{th} highest risk among *n* at risk (for some *j* with $1 \leqq j \leqq n$) at some specified level of confidence with respect to uncertainty—might be calculated directly from predicted risk *R* without distinguishing between uncertain and heterogeneous variates. Indeed, "uncertainty analyses" are often conducted (e.g., see Appendices F and G) in which Monte Carlo techniques are used to approximate *F* in a way that treats all variates in the same manner, without distinguishing those that are uncertain from those that represent interindividual variability. Except for the trivial case in which $n=1$, $F_R(r)$ calculated in this manner can *only* be interpreted as the cdf pertaining to risk to an individual *sampled at random* from the entire population by which $F_R(r)$ was developed.

More typically, regulators might be interested in the (uncertain) risk $\bar{R}$ to an individual who is at average risk relative to others (which is directly related to population risk as described above); more conservatively, interest might lie in the cdf, $F_{R(j)}(r)$, pertaining to (uncertain) risk $R_{(j)} = R_{(qn)}$ to a j^{th} highest or q^{th} quantile (i.e., $100q^{th}$ percentile with respect to variability, not uncertainty) person at risk, where $q = j/n$ and *q* might, for example, be some upper-bound value such as 0.99. In the most conservative risk assessment, interest is focused on uncertain risk $R_{(n)}$ to the person at greatest risk ($q = 1$). Clearly, $R_{(j)} = R$ only if *all* people incur *identical* (although perhaps uncertain) risks.

When both heterogeneous and uncertain variates are involved in the model used to predict *R*, the cdf for $R_{(j)}$ might be difficult to calculate. Some possible approaches are discussed below. If all heterogeneous variates are modeled with distributions truncated at the right-hand tail, $R_{(n)}$ may be approximated simply by using the maximal values of those variates. Thus, in the simple case, $R_{(n)} = U\text{Max}(V)$, and in the complicated case, $R_{(n)} \approx \boldsymbol{H}(\mathbf{U},\mathbf{Max}(\mathbf{V}))$ as a first-order approximation. If truncated distributions are not used for all heterogeneous variates, in which careful and detailed analysis will be needed. Whether or not truncated distributions are used for all input variables, the approximations will be overconservative, perhaps highly so.

$R_{(j)}$ may be described as a *compound* order-statistic, in the sense that the cdf for $R_{(j)}$ has two sources of uncertainty: uncertainty associated with the combined impact of all the uncertain variates used to model *R*, and the more conventional

order-statistic uncertainty associated with sampling the j^{th} highest individual value of R from among a total of n different (but also uncertain) values where these differences arise from all the heterogeneous (as opposed to the uncertain) variates used to model R. For the simple risk model, assuming V and U are statistically independent, it follows that $R_{(j)} = U\,V_{(j)}$ where $V_{(j)}$ is itself an orderstatistic and hence is an *uncertain* quantity that has the following cdf (Kendall and Stuart, 1977):

$$F_{V_{(j)}}(V) = \sum_{k=j}^{n} \binom{n}{k} F_V(v)^j\, 1 - F_V(v)^{n-j} = I_{F_V(v)}(j, n-j+1). \qquad (9)$$

where $F_{V}(v)$ is the cdf modeling heterogeneity in V and where I is the incomplete Beta function. In the case of $j=n$, $F_{V(n)}(v)=\{F_V(v)\}^n$.

The median value of $V_{(n)}$ is thus the $2^{-1/n\,th}$ quantile (i.e., the $100(2^{-1/n})^{th}$ percentile) of V, which is approximately the $\{1-[\mathrm{Ln}(2)/n]\}^{th}$ quantile of V for $n>9$. The "characteristic" value of $V_{(n)}$ is defined as the $[1-(1/n)]^{th}$ quantile of V, which is: the value of V with an "exceedance probability" of $1/n$, the value of V expected to be less than or equal to $V_{(n)}$, the 0.368^{th} (i.e., the e^{-1st}) quantile of $V_{(n)}$, and (generally) also the modal or most likely value of $V_{(n)}$ (Ang and Tang, 1984).

For the more complicated risk model, the ordered risk $R_{(itj)}$ for some or all j may not exist in an unambiguous sense because the cdfs characterizing uncertainty, e.g., in risk R_h and R_k for some particular individuals h and k may intersect one another at one or more probability levels other than 0 and 1 (Bogen, 1990). Although it is always possible to estimate the j^{th} highest "upper-bound" risk among n such R-values (corresponding to n samples from V) all evaluated at some prespecified uncertainty quantile (Bogen, 1990), this approach is generally difficult or impractical to implement by Monte Carol methods for complicated risk models involving both uncertainty and variability. In contrast, it is relatively simple to estimate the j^{th} highest value of expected risk, $\langle R\rangle_{(j)}$; for example for $j=n$ this value is, as noted above, generally most likely to be $F^{-1}/\langle R\rangle\,(1 - n^{-1})$, where $\langle R\rangle \approx H(\langle U\rangle, V)$ may be used as a first-order approximation (see Bogen and Spear, 1987). The ratio $P_n = [F^{-1}/\langle R\rangle\,(1 - n^{-1})]/\langle \bar{R}\rangle$ may thus serve to characterize the magnitude of interindividual variability (or "inequity") in expected individual risks for a population of size n.

Note that unidentifiable person-to-person variability (that is, known values of a quantity that is known to differ among individuals but which values cannot each be assigned to specific individuals) is, for practical purposes, equivalent to pure uncertainty pertaining to those values insofar as the characterization of individual risk is concerned. However, the real distinction between unidentifiable person-to-person variability and true uncertainty is revealed by their different impacts on estimated population risk. In particular, if all other contributions to risk are equal, any positive amount of person-to-person variability in some determinant of risk such as susceptibility—regardless of its identifiability—will

always result in a smaller variance (and thus greater certainty) in corresponding estimated population risk than that resulting from an identically distributed risk determinant whose distribution instead reflects pure uncertainty. For example, if two persons face certain but different risks equal to 0 and 1, respectively (regardless of whether it is known who faces which risk), then the expectation and variance of predicated cases are 1 and 0, respectively; here one case will arise with absolute certainty. However, if both persons face a single uncertain risk equal to 0 or 1 with probability 0.5 and 0.5, respectively, then the expected value of predicted cases is again 1, but its variance is in this case 1; here 0, 1, or 2 cases will arise with probability 0.25, 0.5, and 0.25, respectively.

In general, if n persons face n known risks $p_j = 1,2,\ldots n$, having mean $E(p)$ >0 and variance $Var(p)>0$, then it is well known that, regardless of who faces which particular risk, the expectation and variance of the number N of anticipated cases are $E(N) = nE(p)$ and $Var(N) = n\{E(p)[1-E(p)] - Var(p)\}$, respectively. Now consider the analogous case in which interindividual variability is replaced by pure uncertainty. In this case, all persons face a common but uncertain risk p that is distributed identically to p_j (i.e., $Prob(p=p_j) = 1/n$, $j = 1,2,\ldots n$) and hence has the same mean $E(p)$ and variance $Var(p)$ (where in this case these moments are with respect to uncertainty, not interindividual variability). For this case, it is straightforward to show that again $E(N) = nE(p)$, but that here $Var(N) = n\{(p)[1-E(p)] + (n-1)Var(p)\}$, which exceeds the previous expression for the variance of N by the quantity $n^2Var(p)$.

Summary

In summary, $F_{\bar{R}}(r)$ (characterizing uncertainty in risk to the average person and, approximately, in population risk) and $F_{<R>}(r)$ (characterizing interindividual variability in expected risk) are both easily estimated, even in cases involving complex risk models with uncertain and interindividually variable parameters. These estimates may generally be sufficient for regulatory decisionmaking purposes seeking to address both uncertainty in population risk and differences in individual risk. For example, suppose risk-acceptability criteria were desired to ensure that imposed individual lifetime risks are both de minimis and not grossly inequitable and that 70-year population risk is most likely zero cases. An example of corresponding quantitative criteria might be that the relations $F_{\bar{R}}(10^{-6}) > 0.99$, $p_n > 10^3$, and $F_N(0)<0.50$ should all apply.

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Appendix J

A Tiered Modeling Approach for Assessing the Risks Due to Sources of Hazardous Air Pollutants

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Disclaimer

This report has been reviewed by the Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, and has been approved for publication. Any mention of trade names or commercial products is not intended to constitute endorsement or recommendation for use.

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1.0 Introduction

1.1 Background and Purpose

Title III of the Clean Air Act Amendment of 1990 (CAAA) sets forth a framework for regulating major sources of hazardous (or toxic) air pollutants which is based on the implementation of MACT, the maximum achievable control technology, for those sources. Under this framework, prescribed pollution control technologies are to be installed without the *a priori* estimation of the health or environmental risk associated with each individual source. The regulatory process is to proceed on a source category-by-source category basis, with a list of source categories to be published by the end of 1991, and a schedule for their regulation to be published a year later. After the implementation of MACT, it will be incumbent on the United States Environmental Protection Agency (EPA) to assess the residual health risks to the population near each source within a regulated source category. The results of this residual risk assessment will then be used to decide if further reduction in toxic emissions is necessary for each source category (refer to §112(f) of the CAAA). These decisions will hinge primarily on a determination of the lifetime cancer risk for the "maximum exposed individual" for each source as well as the determination of whether the exposed population near each source is protected from noncancer health effects with an "ample margin of safety". The determination of lifetime cancer risk involves the estimation of long-term ambient concentrations of toxic pollutants whereas the determination of noncancer health effects can involve the estimation of long-term and short-term ambient concentrations.

Since the measurement of long-term and short-term ambient concentrations for each toxic air pollutant (189 pollutants as listed in §112(b)) in the vicinity of each source is a prohibitively expensive task, it is envisioned that the process of residual risk determination would involve performing analytical simulations of toxic air pollutant dispersion for all sources (or a subset of sources) within each source category. Such simulations will subsequently be coupled with health effects information and compared to available data to quantify human exposure, cancer risk, noncancer health risks, and ecological risks.

In addition to mandating the residual risk assessment process, the CAAA provide for the exemption of source categories and pollutants from the MACT-based regulatory process if it can be demonstrated that the risks associated with that source category or pollutant are below specified levels of concern. EPA-approved risk assessments would need to be performed to justify such an exemption, and the CAAA provide for petition processes to approve or deny claims that a source category or a specific pollutant should not be subject to regulation.

The purpose of this document is to provide guidance on the use of EPA-approved procedures which may be used to assess risks due to the atmospheric dispersion of emissions of hazardous air pollutants. It is likely that the techniques described herein will be useful with respect to several decision-making processes associated with the implementation of CAAA Title III (e.g., petition to add or delete a pollutant from the list of hazardous air pollutants, petition to delete a source category from the list of source categories, demonstration of source modification offsets, etc.). In addition, the procedures may serve as the basis for the residual risk determination processes described above. The guidance addresses the estimation of long-term and short-term ambient concentrations resulting from the atmospheric dispersion of known emissions of hazardous air pollutants, and subsequently addresses the techniques currently used to quantify the cancer risks and noncancer risks associated with the predicted ambient concentrations. It describes a tiered approach which progresses from simple conservative screening estimates (provided in the form of lookup tables) to more complex modeling methologies using computer models and site-specific data. In addition to providing guidance to assist in the CAAA Title III implementation process, it is being provided to the general public to assist State and local air pollution control agencies as well as sources of hazardous pollutants in their own assessment of the impacts of these sources.

While the methods described herein comprise the most up-to-date means for assessing the impacts of sources of toxic air pollution, they are subject to future revision as new scientific information becomes available, possibly as a result of the risk assessment methodology study being conducted by the National Academy of Sciences (NAS) under mandate of section 112(o) of the CAAA (report due to Congress from NAS in May, 1993)

1.2 Risk Assessment in Title III

As mentioned above, several provisions of CAAA Title III describe the need to consider ambient concentration impacts and their associated health risks in establishing the regulatory processes for sources of toxic air pollutants. Specifically, these are:

1. A pollutant may be deleted via a petition process from the list of hazardous or toxic pollutants subject to regulation if the petition demonstrates (among other things) that "ambient concentrations…of the substance may not reasonably be anticipated to cause any adverse effects to the human health." (§112(b)(3)(C))
2. A pollutant may be added to the list if a petition demonstrates that "ambient concentrations…of the substance are known or may reasonably be

anticipated to cause to cause adverse effects to human health." (§112(b)(3)(B))

3. An entire source category may be deleted form the list of source categories subject to regulation if a petition demonstrates, for the case of carcinogenic pollutants, that "no source in the category…emits (carcinogenic) air pollutants in quantities which may cause a lifetime risk of cancer greater than one in one million to the individual in the population who is most exposed to emissions of such pollutants from the source," (§112(c)(9)(B)(i)) and, for the case of noncarcinogenic yet toxic pollutants, that "emissions from no source in the category…exceed a level which is adequate to protect public health with an ample margin of safety and no adverse environmental effect will result from emissions from any source." (§112(c)(9)(B)(ii))
4. Within eight years after a source category has been subject to a MACT regulation, EPA must determine whether additional regulation of that source category is necessary based on an assessment of the residual risks associated with the sources in that category. Based on such an assessment, additional regulation of the source category is deemed necessary if "promulgation of such standards is required in order to provide an ample margin of safety to protect the public health" with respect to noncancer health effects, or if the MACT standards "do not reduce lifetime excess cancer risks to the individual most exposed to emissions from a source in the category or subcategory to less than one in one million" with respect to carcinogens, or if a determination is made "that a more stringent standard is necessary to prevent…an adverse environmental effect." (§112(f)(2)(A))

In the context of these provisions, decisions are to be made based on whether or not the predicted impact of a source exceeds some level of concern. For comparison to specified levels of concern, source impacts are quantified in four ways:

1. lifetime cancer risk;
2. Chronic noncancer hazard index;
3. acute noncancer hazard index, and;
4. frequency of acute hazard index exceedances.

These impact measures are discussed in more detail in the next few paragraphs. It is worth noting at this point that insofar as knowledge is available regarding the effects of specific hazardous pollutants on the environment, it may be possible to use ecological hazard index values to quantify such impacts. Such calculations would proceed on a track which is parallel to the calculation of health hazard index values.

For carcinogenic pollutants, the level of concern is the risk of an individual contracting cancer by being exposed to the ambient concentrations of that pollutant over the course of a lifetime, or lifetime cancer risk. For the purposes of §112(c), the criterion specified in the CAAA is 1 in 1,000,000 lifetime cancer risk for the most exposed individual, or the individual exposed to the highest predicted concentrations of a pollutant. (For other purposes, the lifetime cancer risk specifying the level of concern may be higher or lower.) Lifetime cancer risks are calculated by multiplying the predicted annual ambient concentrations (in $\mu g/m^3$) of a specific pollutant by the unit risk factor or unit risk estimate (URE) [1] for that pollutant, where the unit risk factor is equal to the upper bound lifetime cancer risk associated with inhaling a unit concentration (1 $\mu g/m^3$)of that pollutant. Since predicted annual pollutant concentrations around a source vary as a function of position, so do lifetime cancer risk estimates. Thus, decisions involving whether the impact of a source or group of sources is above some level of concern typically focus on the highest predicted concentration (and hence the highest predicted lifetime cancer risk) outside the facility fenceline. The EPA has developed unit risk factors for a number of possible, probable, or known human carcinogens, and will be developing additional cancer unit risk factors as more information becomes available. For the purposes of this document, cancer risks resulting from exposure to mixtures of multiple carcinogenic pollutants will be assessed by summing the cancer risks due to each individual pollutant, regardless of the type of cancer which may be associated with any particular carcinogen.[2]

For pollutants causing noncancer health effects from chronic or acute exposure, the levels of concern are chronic and acute concentration thresholds, respectively, which would be derived from health effects data, taking into account scientific uncertainties. For purposes of estimating potential long-term impacts of hazardous air pollutants, EPA has derived for some pollutants (and will derive for others) chronic inhalation reference concentration (RfC) [1] values, which are defined as estimates of the lowest concentrations of a single pollutant to which the human population can be exposed over a lifetime without appreciable risk of deleterious effects. For purposes of specific chronic noncancer risk assessment, EPA may designate the RfC value, or some fraction or multiple thereof, as the appropriate long-term noncancer level of concern. For purposes of specific acute noncancer risk assessment, the EPA may designate acute reference thresholds as the appropriate short-term noncancer level of concern. For the purposes of this document, long-term noncancer levels of concern will be referred to as chronic concentration thresholds, and short-term noncancer levels of concern will be referred to as acute concentration thresholds. For ease of implementation, acute concentration thresholds will be designated for 1-hour averaging times. This does not necessarily mean that exposure data indicate deleterious health effects from exposure times of 1 hour, but rather that the 1-hour acute

concentration threshold has been derived such that it is protective of the exposure duration of concern.

The risk with respect to long- or short-term deleterious noncancer health effects associated with exposure to a pollutant or group of pollutants is quantified by the hazard index. The chronic noncancer hazard index is calculated by dividing the modeled annual concentration of a pollutant by its chronic concentration threshold value. The acute noncancer hazard index is calculated by dividing the modeled 1-hour concentration of a pollutant by its acute concentration threshold value. If multiple pollutants are being evaluated, the (chronic or acute) hazard index at any location is calculated by dividing each predicted (annual or 1-hour) concentration at that location by its (chronic or acute) concentration threshold value and summing the results.[2] If the hazard index is greater than 1.0, this represents an exceedance of the level of concern at that location. For pollutants which can cause deleterious health effects from acute exposures, exceedances of a level of concern may occur at any location and at any time throughout the modeling period. Thus, the frequency with which any location experiences an exceedance also becomes a measure of the risk associated with a modeled source. Frequency of acute hazard index exceedances is only addressed by the most refined analysis methods referred to in this document.

Information on UREs and RfCs is accessible through the Integrated Risk Information System (IRIS), EPA Environmental Criteria and Assessment Office (ECAO) in Cincinnati, Ohio, (513) 569-7254.

1.3 Overview of Document

This document is divided into three major sections, each section addressing a different level of sophistication in terms of modeling, referred to as "tiers". The first tier is a simplified screening procedure in which the user can estimate maximum off-site ground-level concentrations without extensive knowledge regarding the source and without the need of a computer. The second tier is a more sophisticated screening technique which requires a bit more detailed knowledge concerning the source being modeled and, in addition, requires the execution of a computer program. The third tier involves site-specific computer simulations with the aid of computer programs and detailed source parameters. Since the effects of toxic air pollutants may be of concern from both a long-term and a short-term perspective, each tier is divided into two parts. The first part addresses dispersion modeling to assess long-term ambient concentrations (important from a cancer-causing or chronic noncancer effects standpoint) and the second addresses dispersion modeling for the estimation of short-term concentrations (important from an acute toxicity perspective).

It should be noted that this document is intended to be used in conjunction with the User's Guides for the models described: SCREEN,[3] TOXST,[4] and TOXLT.[5] It is not intended to replace or reproduce the contents of these documents. In addition, the reader may wish to consult the "Guideline on Air Quality Models (Revised)"[6] for more detailed information on the consistent application of air quality models. Modelers may also wish to use the EPA's TSCREEN[7] modeling system to assist in the Tier 2 computer simulation of certain toxic release scenarios. It should be noted, however, that toxic pollutant releases which TSCREEN treats as heavier-than-air are not to be modeled using techniques described herein. Atmospheric dispersion of such pollutants requires a more refined analysis, such as those described in Reference[8] . Model codes, user's guides, and associated documentation referred to in this document can be obtained through the Technology Transfer Network (TTN) of the EPA's Office of Air Quality Planning and Standards (OAQPS), and access information is provided in Appendix A.

The modeling tiers are designed such that the concentration estimates from each tier should be less conservative than the previous one. This means that, for a given situation, a Tier 1 modeled impact should be greater than, or more conservative than, the Tier 1 modeled impact, and the Tier 2 modeled impact should be more conservative than the Tier 3 modeled impact. Progression from one tier of modeling to the next thus involves the use of levels of concern, as defined above. For example, if the results of a Tier 1 analysis indicates an exceedance of a level of concern with respect to either (1) the maximum predicted cancer risk, (2) the maximum predicted chronic noncancer hazard index, or (3) the maximum predicted acute hazard index, the analyst may wish to perform a Tier 2 analysis. If all three of these impact measures are below their specified levels of concern, there should be no need to perform a more refined simulation, and thus, there should be no need to progress to the next tier of modeling. Since the establishment of levels of concern for each specific hazardous air pollutant is not a part of this effort, this document will refer to generic levels of concern, and users will need to consult subsequent EPA documents to determine the specific levels of concern for their particular pollutant or pollutant mixture and for the particular purpose of their modeling efforts.

1.4 General Modeling Requirements, Definitions, and Limitations

This document describes modeling methologies for point, area, and volume sources of atmospheric pollution. A point source is an emission which emanates from a specific point, such as a smokestack or vent. An area source is an emission which emanates from a specific, well-defined surface, such as a lagoon, landfarm, or open-top tank. Sources referred to as having "fugitive" emissions (e.g., multiple leaks within a specific processing area) are typically modeled

as area sources. The methods used in this document are generally considered to be applicable for assessing impacts of a source from the facility fenceline out to a 50 km radius of the source or sources to be modeled. There is no particular upper or lower limit on emission rate value for which these techniques apply.

For the purposes of this document, "source" means the same thing as "release", and "air toxic" means the same as "hazardous air pollutant". It should be noted that "area source" as defined in the previous paragraph is not the same as the "area source" defined by the CAAA. Modeling techniques described in this document are specifically intended for use in the simulation of a finite number of well-defined sources, not for simulation of a large number of ill-defined small sources distributed over a large region, as might well be the case for some "area sources" specified in the CAAA. Simulation of the acute and chronic impacts of such area sources may utilize the RAM model[9] and the CDM 2.0 model,[10] respectively. Consult the "Guideline on Air Quality Models (Revised)"[6] for additional information. The reader should note that relatively small, well-defined groups of sources, however, may be modeled using the techniques described herein.

This document does not address the simulation of facilities located in complex terrain. Those interested in modeling facilities with possible complex terrain effects are directed to consult the "Guideline on Air Quality Models (Revised)"[6] or their EPA Regional Office modeling contact for assistance in this area (see listing Appendix B).

In order to conduct an impact assessment, it is necessary to have estimates of emission rates of each pollutant from each source or release point being included in the assessment. Emission rates may be best estimated from experimental measurements or sampling, where such test methods are available. Alternatively, mass balance calculations or use of emission factors developed for specific types of processes may be used to quantify emission rates. The procedures discussed in this document do not address the emission estimation process. Guidance for source-specific emission rate estimation and emission test methods is available in other EPA documentation (e.g., see References 11 through 15). Additional information concerning specific emission measurement techniques is available through the OAQPS TTN (see Appendix A).

Since many sources of hazardous air pollutants are intermittent in nature (e.g., batch process emissions), the techniques in this document have been developed to allow the treatment of intermittent sources as well as continuous types of sources. It is important to understand the different treatment of emission rates for both types of sources when carrying out either the analysis of a long-term

impact or a short-term impact. In a long-term impact analysis, the emission rate used for modeling is based on the amount of pollutant emitted over a 1-year period, regardless of whether the emission process is a continuous or intermittent one. In addition, to assess the worst-case impact of a source or group of sources, long-term emission rates used in model simulations should reflect the emission rates for a plant or process which is operating at full design capacity. In a short-term impact analysis, the emission rate used for modeling is based on the maximum amount of pollutant emitted over a 1-hour period, during which the source is emitting. The Tier 1 and Tier 2 procedures evaluate the combined worst-case impacts of intermittent sources as if they are all emitting at the same time, whereas the Tier 3 procedures incorporate a more realistic treatment of intermittent sources by turning them on and off throughout the simulation period according to user-specified frequency of occurrence of each release. This frequency of occurrence should reflect the normal operating schedule of the source when operating at maximum design capacity.

In addition to emission rate estimates, it is necessary to have quantitative information about the sources to conduct a detailed impact assessment. Tier 1 analyses require information about the height of the release above ground level and the shortest distance from the release point to the facility fenceline. Higher tiers of analysis require additional information including, but not limited to:

Stack height
Inside stack diameter
Exhaust gas exit velocity
Exhaust gas exit temperature
Dimensions of structures near each source
Dimensions of ground-level area sources
Exact release and fenceline location
Exact location of receptors for determining worst-case impacts
Land use near the modeled facility
Terrain features near the facility
Duration of short-term release
Frequency of short-term release

Where appropriate, this document will address the best means of obtaining these input data. In some more complex cases, the modeling contact at the nearest EPA Regional Office may need to be consulted for specific modeling guidance (see listing in Appendix B).

Depending on the specific purpose of the impact assessment, it may be difficult for the modeler to decide which sources (or release points) and which pollutants should be included in a particular analysis or simulation. Since these

questions pertain to the particular purposes for which the impact assessment is being performed, they are not addressed by this document. Instead, this document refers to and provides guidance for modeling various scenarios including single-source, multiple-source, single-pollutant, and multiple-pollutant scenarios. Subsequent EPA documents will address the questions of which sources and which pollutants should be included in an impact analysis for a specific regulatory purpose.

2.0 Tier I Analyses

2.1 Introduction

Tier 1 analysis of a stationary source (or group of sources) of toxic pollutant(s) is performed to address the question of whether or not the source has the potential to cause a significant impact. This "screening" analysis is performed by using tables of lookup values to obtain the "worst-case" impact of the source being modeled. The analysis is performed to assess both the potential long- and short-term impacts of the source. If the predicted screening impacts are less than the appropriate levels of concern, no further modeling is indicated. If the predicted screening impacts are above any levels of concern, further analysis of those impacts at a higher Tier may be desireable to obtain more accurate results.

The Tier 1 "lookup tables" have been created as tools which may be easily used to estimate conservative impacts of sources of toxic pollutants with a minimal amount of information concerning those sources. The normalized annual and 1-hour concentration tables were created based on conservative simulations of toxic pollutant sources with the EPA's SCREEN model.[3] In this context, "conservative" simulations use conservative assumptions regarding meteorology, building downwash, plume rise, etc. Conservative annual concentrations were derived from SCREEN 1-hour estimates using the conservative multiplication factor of 0.10.

2.2 Long-term Modeling

Long-term modeling of toxic or hazardous air pollutants is aimed at the estimation of annual average pollutant concentrations to which the public might be exposed as the result of emissions from a specific source or group of sources. From the EPA regulatory viewpoint, this "public" does not include employees of the facility responsible for the emissions (this is the jurisdiction of the Occupational Safety and Health Agency, OSHA). Thus, the impact assessment focuses on estimating concentrations "off-site", or outside the facility boundary. For carcinogens, the calculation of cancer risk proceeds by multiplying annual concentrations by pollutant-specific cancer potency factors derived from health effects data. The impacts of pollutants with chronic noncancer effects are generally assessed by comparing predicted annual concentrations with chronic threshold concentrations which are again derived from experimental health data. For the purposes of protecting the general public against "worst-case" pollutant concentrations, the analysis is focused on predicting the worst-case, or maximum annual average concentrations.

2.2.1 Maximum Annual Concentration Estimation

A long-term tier 1 analysis requires the following information:

1. annual average emission rate of each pollutant from each source included in the simulation (T/yr). These emissions do not have to be continuously emitted, but rather should represent the total amount of pollutant which is generated by this source in a year. Note that the tons used in this regard are English tons (1 T. = 2000 lb.) Also note that, for Tier 1 analyses, the emission rate from an area source represents the total emissions from the area, not the emissions per square unit area.
2. height of the release point above ground (m), for each point source.
3. source types (point or area). Point sources typically include exhaust vents (pipes or stacks), or any other type of release that causes toxic materials to enter the atmosphere from a well-defined location, at a well-defined rate. Area sources may also be well-defined, but differ from point sources in that the extent over which the release occurs is substantial.
4. maximum horizontal distance across each area source (m).
5. nearest distance to property line (m). Concentration estimates are needed at locations that are accessible to the general public. This is typically taken to be any point at or beyond the property-line of a facility. Estimate the distance from the point of each release to the nearest point on the fenceline. (This need not be the same fenceline point for each release). If the source is characterized as an area source, this distance should be measured from the nearest edge of the area source, not from the center.

Once these five items are determined for each release (or source), screening estimates of normalized maximum annual concentrations resulting from each release are obtained from Table 1 using the following procedure.

1. For an area source, select the "side length" in the table (10m, 20m, 30m) which is less than or equal to the maximum horizontal distance across the source.
2. For a point source, select the largest "emission height" in the table (0m, 2m, 5m, 10m, 35m, or 50m) that is less than or equal to the estimated height of release.
3. Select the largest distance in the table (10m, 30m, 50m, 100m, or 200m) that is less than or equal to the nearest distance to the property-line.
4. Take the appropriate normalized maximum annual concentration for this release height and distance from the table, and multiply by the emission rate

TABLE 1. NORMALIZED MAXIMUM ANNUAL CONCENTRATIONS ($\mu g/m^3$)/(T/yr)

Source type[a]	Emission height, m	Side length,[b] m	Normalized maximum concentrations at or beyond[c] 10m	30m	50m	100 m	20 m	500 m
A	0	10	9.56E+2	3.02E+2	1.64E+2	6.48E+1	2.32E+1	5.53E+0
A	0	20	5.15E+2	1.83E+2	1.07E+2	4.78E+1	1.91E+1	5.04E+0
A	0	30	3.51E+2	1.31E+2	7.92E+1	3.74E+1	1.61E+1	4.58E+0
P	0	—	5.41E+3	7.92E+2	3.25E+2	9.67E+1	2.91E+1	6.08E+0
P	2	—	1.87E+2	1.42E+2	1.35E+2	7.28E+1	2.64E+1	5.96E+0
P	5	—	9.62E+1	7.46E+1	5.18E+1	2.72E+1	1.48E+1	5.18E+0
P	10	—	2.77E+1	2.44E+1	2.11E+1	1.36E+1	7.17E+1	2.88E+0
P	20	—	6.91E+0	4.52E+0	4.52E+0	3.80E+0	2.44E+0	1.06E+0
P	35	—	2.26E+0	2.26E+0	1.13E+0	1.11E+0	8.98E-1	4.41E-1
P	50	—	1.11E+0	1.10E+0	1.11E+0	4.69E-1	4.23E-1	2.53E-1

[a]Source type P=Point Source, type A=Area source
[b]Side length of square area source
[c]Distance downwind of an area source indicates distance from downwind edge of the area source.

4. of each toxic substance (t/yr) in the release to obtain the concentration estimate (μg/m^3). DO NOT INTERPOLATE TABLE VALUES.

For example, consider the situation in which a toxic pollutant A is released at a rate of 11.6 T/yr from a vent-pipe that is 40m tall, and which is attached to a building that is 4m tall, 10m long, and 5m wide. The nearest boundary of the facility is located 65m from the pipe. A value of 35m should be selected for the emission height, because all larger entries in the table exceed the actual height of release of 40m. Concentrations should be estimated for a distance of 50m, because once again, all greater entries in the table exceed the actual distance of 45m. The appropriate normalized maximum annual concentration is 1.13 (μg/m^3)(T/yr). Multiplying by the emission rate of 14.6 T/yr results in a maximum annual concentration estimate for screening purposes equal to 16.5 μg/m^3.

2.2.2 Cancer risk assessment

Once the maximum annual concentration has been estimated for each release being modeled, upper bound lifetime individual cancer risk may be estimated by multiplying the maximum annual concentration estimates of each carcinogenic pollutant by the unit cancer risk factor for that pollutant and then summing results. This approach assumes that all cancer risks are additive, regardless of the organ system which may be affected. It should be noted that this approach assumes that all worst-case impacts occur at the same location. While this assumption may not be very realistic, it does help to insure that Tier 1 results are conservative, and, therefore protective of the public.

As an example of this approach, suppose one is simulating a plant which emits 2 pollutants A and B, through 4 different stacks such that pollutant A is released from stacks 1 and 2, and pollutant B is released from stacks 2, 3, and 4. In this example, stack 1 is the same as that described in the example above. After going through the above procedure to estimate the maximum annual concentrations of each pollutant from each stack, the results are:

Source	Compound	Max impact
Stack 1	Pollutant A	16.5 μg/m^3
Stack 2	Pollutant A	5.49 μg/m^3
Stack 2	Pollutant B	2.35 μg/m^3
Stack 3	Pollutant B	4.13 μg/m^3
Stack 4	Pollutant B	24.9 μg/m^3

Suppose that the unit cancer risk factors for pollutants A and B are know to be 1.0×10^{-7} and 2.0×10^{-7} $(\mu g/m^3)^{-1}$, respectively. The Tier 1 maximum cancer

risk is calculated for the individual releases and pollutants and summed as follows:

Source	Compound	Max impact	Max risk
Stack 1	Pollutant A	16.5 μg/m^3	1.65×10^{-4}
Stack 2	Pollutant A	5.49 μg/m^3	5.49×10^{-7}
Stack 2	Pollutant B	2.35 μg/m^3	4.70×10^{-7}
Stack 3	Pollutant B	4.13 μg/m^3	8.26×10^{-7}
Stack 4	Pollutant B	24.9 μg/m^3	4.98×10^{-4}
		Total risk	8.48×10^{-4}

If we are assessing the impact of this group of sources in relation to the CAAA specified level of concern of 1×10^{-4} lifetime cancer risk, and since the maximum Tier 1 risk is greater than the CAAA specified concern level of 1×10^{-4}, this source warrants further modeling on the basis of cancer risk (note that this does not rule out the need to investigate acute or chronic nonccancer risk).

2.2.3 Chronic Noncancer Risk Assessment

For all pollutants which pose a chronic noncancer threat to health, an assessment of the magnitude of this threat is made using the hazard index approach. The chronic noncancer hazard index is calculated by summing the maximum annual concentrations for each pollutant divided by the chronic threshold concentration value for that pollutant. if the calculated hazard index is greater than 1.0, the release or releases being simulated may pose a threat to the public, and further modeling may be indicated. It should again be noted that, for the sake of erring conservatively, this approach assumes that the worst-case impacts of all releases occur at the same location.

As an example of the above procedure, suppose that pollutants A and B in the example above pose a chronic noncancer health risk, and their respective chronic concentration threshold values are 20.0 and 5.0 μg/m3, respectively. The chronic noncancer hazard index would be formulated as follows:

Source	Compound	Max. Impact	Hazard Index
Stack 1	Pollutant A	16.5 μg/m^3	0.825
Stack 2	Pollutant A	5.49 μg/m^3	0.275
Stack 2	Pollutant B	2.35 μg/m^3	0.470
Stack 3	Pollutant B	4.13 μg/m^3	0.826
Stack 4	Pollutant B	24.9 μg/m^3	4.980
		Total Hazard index	7.376

In this case, one of the individual hazard index values exceeds 1.0, the total hazard index for this modeled facility exceeds 1.0, and further modeling at a higher Tier may be desired.

2.3 Short-term Modeling

Since short-term modeling of toxic or hazardous air pollutants is aimed at the estimation of 1-hour average pollutant concentrations to which the public might be exposed as the result of emissions from a specific source or group of sources. Again, from the EPA regulatory viewpoint, this "public" does not include employees of the facility responsible for the emissions (this is the jurisdiction of OSHA). Thus, the impact assessment focuses on estimating concentrations "off-site", or outside the facility boundary. From the short-term perspective, the health effects of most concern vary, but they are those which create detrimental health effects as the result of short-term exposure to toxic pollutants. The risks associated with such exposures are generally assessed by comparing 1-hour predicted concentrations with acute threshold concentrations which are derived from experimental health data. For the purposes of protecting the general public against "worst-case" pollutant concentrations, the analysis is focused on predicting the worst-case, or maximum 1-hour average concentrations.

2.3.1 Maximum Hourly Concentration Estimation

A short-term Tier 1 analysis requires the following information:

1. maximum 1-hour average emission rate of each pollutant from each source included in the simulation (g/s). If the release is a continuous, constant-rate emission, then this value is equivalent to the release rate for long-term modeling, except that it is expressed in g/s instead of T/yr. (To convert from T/yr to g/s, divide by 34.73; to convert from g/s to T/yr, multiply by 34.73) If the release is intermittent, such as a batch process, this value is equivalent to the maximum number of grams emitted during any hour when the release is occurring divided by 3600. Again note that, for Tier 1 analyses, the emissions from an area source represent the total emissions from that source, not just the emissions per unit area surface.
2. height of each release above ground (m), for point sources.
3. source types (point or area). Point sources typically include exhaust vents (pipes or stacks), or any other type of release that causes toxic materials to enter the atmosphere from a well-defined location, at a well-defined rate. Area sources may also be well-defined, but differ from point sources in that the extent over which the release occurs is substantial.
4. maximum horizontal distance across each area source (m).

5. nearest distance to property-line (m). Concentration estimates are needed at locations that are accessible to the general public. This is typically taken to be any point at or beyond the property-line of a facility. Estimate the distance from the point of each release to the nearest point on the fence-line. (This need not be the same fenceline point for each release). If the source is characterized as an area source, this distance should be measured from the nearest edge of the area source, rather than from the center of the area source.

Once these five items are determined for each release, screening estimates of maximum 1-hour average concentrations resulting from each release are obtained from Table 2 using the following procedure.

1. For an area source, select the "side length" in the table (10m, 20m, 30m) which is less than or equal to the maximum horizontal distance across the source.
2. For point sources, select the largest "emission height" in the table (0m, 2m, 5m, 10m, 35m, or 50m) that is less than or equal to the estimated height of release.
3. For each source, select the largest distance in the table (10m, 20m, 50m, 100m, or 200m) that is less than or equal to the nearest distance to the property-line.
4. Take the normalized maximum 1-hour concentration for this release and fenceline distance, and multiply by the emission rate of each toxic pollutant (g/s) in the release to obtain the maximum off-site 1-hour average concentration estimates ($\mu g/m^3$). DO NOT INTERPOLATE TABLE VALUES.

For example, again consider the situation in which toxic material A is released from a vent-pipe that is 40m tall, and which is attached to a building that is 4m tall, 10m long, and 5m wide. The nearest boundary of the facility is located 65m from the pipe. For the short-term assessment, it has been determined that the maximum emissions of A that can occur during any hour of the year is 1800g, therefore the emission rate for short-term assessment is 1800g/3600s = 0.50g/s. A value of 35m is again selected for the emission height, because all larger entries in the table exceed the actual height of release. Concentrations are estimated for a distance of 50m, because once again, all greater entries in the table exceed the actual distance of 65m. The appropriate normalized maximum 1-hour average concentration is 3.94E = 2 $(\mu g/m^3)/(g/s)$. Multiplying by the emission rate of 0.50g/s results in a maximum hourly concentration estimate for screening purposes equal to 197 $\mu g/m^3$.

TABLE 2. NORMALIZED MAXIMUM 1-HOUR AVERAGE CONCENTRATIONS (μg/m3)/(g/s)

Source type[a]	Emission height, m	Side length,[b] m	Normalized maximum concentrations at or beyond[c]					
			10m	30m	50m	100 m	20 m	500 m
A	0	0	3.32E+5	1.05E+5	5.70E+4	2.25E+4	8.07E+3	1.92E+3
A	0	20	1.79E+5	6.36E+4	3.72E+4	1.66E+4	6.62E+3	1.75E+3
A	0	30	1.22E+5	4.54E+4	2.75E+4	1.30E+4	5.59E+3	1.59E+3
P	0	—	1.88E+6	2.75E+5	1.13E+5	3.36E+3	1.01E+4	2.11E+3
P	2	—	6.51e+4	4.92E+4	4.69E+4	2.53E+4	9.18E+3	2.07E+3
P	5	—	3.34E+4	2.59E+4	1.80E+4	9.44E+3	5.13E+3	1.80E+3
P	10	—	9.61E+3	8.49E+3	7.36E+3	4.71E+3	2.49E+3	1.00E+3
P	20	—	2.45E+3	1.57E+3	1.57E+3	1.32E+3	8.46E+2	3.67E+2
P	35	—	7.84E+2	7.84E+2	3.94E+2	3.85E+2	3.12E+2	1.53E+2
P	50	—	3.84E+2	3.84E+2	3.84E+2	1.63E+2	1.47E+2	8.77E+2

[a] Source type P=Point Source, type A=Area source

[b] Side length of square area source

[c] Distance downwind of an area source indicates distance from downwind edge of the area source.

2.3.2 Acute Hazard Index Assessment

For all pollutants which pose a threat to health based on acute exposure, an assessment of the magnitude of this threat is made using the acute hazard index approach, similar to that used in chronic noncancer risk assessment. In this case, however, the acute hazard index is calculated by summing the maximum 1-hour concentrations for each pollutant divided by the acute concentration threshold value for that pollutant. It should again be noted that, for the sake of erring conservatively, this approach assumes that the worst case impacts of all releases can occur simultaneously at the same location. Similar to the chronic risk assessment, if the calculated hazard index is greater than 1.0, the release or releases being simulated may pose a threat to the public, and further modeling at a higher Tier may be indicated.

As an example of the acute hazard index approach, consider the same plant being simulated in Section 2.2.2, but this time the maximum 1-hour concentrations are determined using the procedure in Section 2.3.2 to be the following:

Source	Compound	Max. 1-hr impact
Stack 1	Pollutant A	197 μg/m^3
Stack 2	Pollutant A	257 μg/m^3
Stack 2	Pollutant B	110 μg/m^3
Stack 3	Pollutant B	301 μg/m^3
Stack 4	Pollutant B	367 μg/m^3

Further suppose that pollutants A and B pose health problems from acute exposures with acute threshold concentration values of 200 and 100 μg/m^3, respectively. The acute hazard index is calculated as follows:

Source	Compound	Max. 1-hr impact	Hazard Index
Stack 1	Pollutant A	197 μg/m^3	0.985
Stack 2	Pollutant A	257 μg/m^3	1.285
Stack 2	Pollutant B	110 μg/m^3	1.100
Stack 3	Pollutant B	301 μg/m^3	3.010
Stack 4	Pollutant B	367 μg/m^3	3.670
		Total Hazard Index	10.050

In this case, 4 of the individual hazard index values exceeds 1.0, the total hazard index for the modeled plant exceeds 1.0, and further modeling at a higher Tier may be desired.

3.0 TIER 2 ANALYSES

3.1 Introduction

Tier 2 analysis of a stationary source (or group of sources) of toxic pollutant(s) may be desired if the results of a Tier 1 analysis indicate an exceedance of a level of concern with respect to one or more of the following: (1) the maximum predicted cancer risk; (2) the maximum predicted chronic noncancer hazard index, or; (3) the maximum predicted acute hazard index. Note that in situations where only one or two of the Tier 1 criteria are exceeded, only those analyses which exceed the Tier 1 criteria may need to be performed at the higher Tier. For example, if the Tier 1 analysis showed cancer risk and chronic noncancer risks to be of concern while the acute risk analysis showed no cause for concern, only long-term modeling for cancer risk and noncancer risk may need to be performed at Tier 2. Tier 2 analyses are slightly more sophisticated than Tier 1 analyses, and therefore require additional input information as well as a computer for their execution. Tier 2 analyses are structured around the EPA's SCREEN model and its corresponding documentation entitled "Screening Procedures for Estimating the Air Quality Impact of Stationary Sources."[3] The SCREEN model source code and documentation is available through the OAQPA TTN (see Appendix A).

Again, similar to the Tier 1 analysis, if any of the predicted model impacts from Tier 2 are above the appropriate levels of concern, further modeling is indicated at a higher Tier.

3.2 Long-term Modeling

Long-term Tier 2 modeling utilizes the SCREEN[3] model to estimate 1-hour maximum concentrations, and then utilizes a conservative conversion factor to derive maximum annual concentration values from the SCREEN predictions.[16, 17] These maximum annual concentration estimates are used to assess cancer risk and chronic noncancer risk exactly as in Section 2.2.2 and 2.2.3 of this document.

3.2.1 Maximum Annual Concentration Estimation

In addition to the information required to perform a Tier 1 analysis, a Tier 2 analysis requires the following information:

1. the inside diameter of the stack at the exit point (m).
2. the stack gas exit velocity (m/s)
3. the stack gas exit temperature (K)

4. a determination of whether the area surrounding the modeled facility is urban or rural. This is usually assessed on the basis of land use in the vicinity of the facility.

   Refer to the "Guideline on Air Quality Models (Revised)"[6] for additional guidance on this determination.

5. downwash potential. Downwash effects must be included in dispersion estimates for point (stack) sources wherever the point of release is located on the roof of a building or structure, or within the lee of a nearby structure. The potential for downwash is determined in the following way. First, estimate the heights and maximum horizontal dimensions[*] of the structures nearest the point of release. For each structure, determine which of these two dimensions is less, and call this length L. If the structure is less than 5L away from the source, then this structure may cause downwash. For every structure satisfying this criterion, calculate a height by multiplying L by 1.5, and adding this to the actual height of the structure. If any calculated height exceeds the height of the release, then downwash calculations must be made for that release.

Once these items are determined for each release being modeled, estimates of maximum concentrations from each release are obtained through individual SCREEN runs for each release. Recommendations for each SCREEN run are as follows:

1. The emission rates used for Tier 1 long-term modeling should be converted from T/yr to g/s (divide T/yr by 34.73). Area source emission rates should be converted to g/s/m2 by dividing the total area of the source.
2. Choose the default atmospheric temperature of 293K
3. For each release, exercise the automated distance array choosing as the minimum receptor distance the appropriate nearest fenceline distance for that release, and choosing 50 km as the maximum receptor distance. The maximum concentration for that release will then be chosen as the maximum at or beyond the nearest fenceline distance.
4. The option for flagpole receptors should not be used.

[*] Note: The maximum horizontal dimension is defined as the largest possible alongwind distance the structure could occupy.

5. For each release, the maximum 1-hour concentration should be noted.
6. Maximum annual concentrations should be calculated for each release by multiplying predicted maximum 1-hour concentrations by 0.08.

As an example of the Tier 2 long-term analysis, consider Stack 1 from the Tier 1 example. To consider downwash possibilities, the maximum horizontal dimension is first estimated as $\{(10m)^2 + (5m)^2\}^{1/2} = 11.2m$. The dimension L is then 4m, and the maximum stack height for which downwash is possible would be 4m + 1.5 × 4m = 10m. Since the actual stack height is 40m, downwash need not be considered in the SCREEN simulation. The emission rate specified in the example of 14.6 T/yr is converted to g/s to be used in the SCREEN simulation, resulting in an emission rate of 14.6/34.73 = 0.42 g/s. In addition to the actual stack height (40m) and minimum fenceline distance (65m), input parameters for the SCREEN simulation are:

Inside stack diameter	0.5m
Stack gas exit velocity	5.6m/s
Stack gas exit temperature	303 K
Plant Location	urban

The results from the SCREEN simulation indicates that the maximum 1-hour concentration at or beyond 65m is 32.5 $\mu g/m^3$, occurring 165m downwind. Using the recommended conversion factor of 0.09, the maximum annual concentration is estimated at 2.6 $\mu g/m^3$ (this value can be contrasted with the Tier 1 estimation of 16.5 $\mu g/m^3$).

3.2.2 Cancer Risk Assessment

Maximum annual concentrations for all releases of carcinogens should be multiplied by the appropriate unit cancer risk factor and summed to estimate the maximum cancer risk. It should be noted that this approach, as in Tier 1, presumes that all worst-case impacts occur at the same location. While this assumption may not be very realistic, it does help insure that the results of a Tier 2 analysis are conservative and therefore protective of the public. More receptor-specific risk calculations are addressed in the Tier 3 analyses.

Borrowing again from the Tier 1 example, maximum annual impacts for each source and pollutant combination are estimated using the SCREEN model. Risk estimates are then made by summing the risk due to each release, regardless of downwind distance to maximum impact. The results are:

Source	Compound	Max. Impact	Max risk
Stack 1	Pollutant A	2.60 μg/m^3	2.60×10^{-7}
Stack 2	Pollutant A	1.34 μg/m^3	1.34×10^{-7}
Stack 2	Pollutant B	0.58 μg/m^3	1.16×10^{-7}
Stack 3	Pollutant B	0.62 μg/m^3	1.24×10^{-7}
Stack 4	Pollutant B	3.70 μg/m^3	7.40×10^{-7}
		Total Risk	1.38×10^{-6}

For this example, the maximum lifetime cancer risk estimated using the Tier 2 methods is a factor of 6 lower than that estimated in the Tier 1 analysis. However, the cancer risk level still exceeds 1×10^{-6}, indicating that modeling at a higher Tier may be desirable.

3.2.3 Chronic Noncancer Risk Assessment

As in Tier 1, maximum annual concentrations are divided by their chronic concentration threshold values and summed to calculate the hazard index values. Again, this approach conservatively assumes that all worst-case impacts occur at the same location.

Continuing with the example, the chronic noncancer hazard index is recalculated using the Tier 2 estimated long-term impacts. Threshold concentration values for chronic noncancer effects again are taken as 20.0 and 5.0 μg/m^3 for pollutants A and B, respectively. The following results:

Source	Compound	Max. Impact	Hazard Index
Stack 1	Pollutant A	2.60 μg/m^3	0.130
Stack 2	Pollutant A	1.34 μg/m^3	0.067
Stack 2	Pollutant B	0.58 μg/m^3	0.116
Stack 3	Pollutant B	0.62 μg/m^3	0.124
Stack 4	Pollutant B	3.70 μg/m^3	0.740
Total Hazard Index			1.177

The chronic noncancer hazard index estimated in Tier 2 is a good deal less than that estimated for the same sources in Tier 1. Even though none of the individual source/pollutant combinations exceeds a chronic threshold concentration value, the total hazard index exceeds 1.0, and further analysis at Tier 3 is indicated for chronic noncancer effects.

3.3 Short-term Modeling

Short-term Tier 2 modeling utilizes the SCREEN[3] model to estimate 1-hour maximum concentrations directly. These maximum 1-hour concentration estimates are used to assess acute hazard index values exactly as in Section 2.3.2 of this document.

3.3.1 Maximum Hourly Concentration Estimation

In addition to the information required to perform a Tier 1 short-term analysis, a Tier 2 analysis requires the following information for stack sources:

1. the inside diameter of the stack at the exit point (m).
2. the stack gas exit velocity (m/s)
3. the stack gas exit temperature (K)
4. a determination of whether the area surrounding the modeled facility is urban or rural. This is usually assessed on the basis of land use in the vicinity of the facility. Refer to the "Guideline on Air Quality Models (Revised)"[6] for additional guidance on this determination.
5. downwash potential. Downwash effects must be included in dispersion estimates for point sources whenever the point of release is located on the roof of a building or structure, or within the lee of a nearby structure. The potential for downwash is determined in the following way. First, estimate the heights and maximum horizontal dimensions of the structures nearest the point of release. For each structure, determine which of these two dimensions is less, and call this length L. If the structure is less than 5L away from the source, then this structure may cause downwash. For every structure satisfying this criterion, calculate a height by multiplying L by 1.5, and adding this to the actual height of the structure. If any calculated height exceeds the height of the release, then downwash calculations must be made for that release.

Once these items are determined for each release being modeled, estimates of maximum concentrations from each release are obtained through individual SCREEN runs for each release. Recommendations for each SCREEN run are as follows:

1. Choose the default atmospheric temperature of 293K.
2. Area source emission rates reflect the total emission rate from divided by the area of the source.

3. For each release, exercise the automated distance array choosing as the minimum receptor distance the appropriate nearest fenceline distance for that release, and choosing 50 km as the maximum receptor distance. The maximum concentration for that release will then be chosen as the maximum at or beyond the nearest fenceline distance.
4. The option for flagpole receptors should not be used.
5. For each release, the maximum 1-hour concentration should be noted.

Using this approach with the Stack 1 example, the SCREEN model is exercised with the stack parameters specified in Section 3.2.1. The maximum short-term emission rate of 0.50 g/s (see Section 2.3.1), however, is used to estimate the maximum 1-hour source impact. The results of the SCREEN model indicate that the maximum 1-hour concentration is 38.8 µg/m3, again occurring 165m downwind.

3.3.2 Acute Hazard Index Assessment

As in Tier 1, maximum 1-hour concentrations are divided by their acute threshold concentration values and summed to calculate the acute hazard index values. Again, this approach conservatively assumes that all worst-case impacts can occur simultaneously at the same location.

To illustrate this procedure, short-term impacts from the example plant are assessed using the hazard index approach. Again the acute threshold concentration values are taken as 200 and 100 µg/m3, respectively. The results are:

Source	Compound	Max. 1-hr impact	Hazard Index
Stack 1	Pollutant A	34.8 µg/m^3	0.174
Stack 2	Pollutant A	70.5 µg/m^3	0.352
Stack 2	Pollutant B	29.9 µg/m^3	0.299
Stack 3	Pollutant B	50.0 µg/m^3	0.500
Stack 4	Pollutant B	60.4 µg/m^3	0.604
Total Hazard Index			1.925

For this example, the acute hazard index estimated in Tier 2 is roughly 20% of that estimated for the same sources in Tier 1. However, since the total hazard index exceeds 1.0, further analysis at Tier 3 is indicated for health effects resulting from acute exposures.

4.0 Tier 3 Analyses

4.1 Introduction

Tier 3 analysis of a stationary source (or group of sources) of toxic pollutant(s) may be desired if the results of a Tier 2 analysis indicate an exceedance of a level of concern with respect to one or more of the following: (1) the maximum predicted cancer risk; (2) the maximum predicted chronic noncancer hazard index, or; (3) the maximum predicted acute hazard index. Tier 3 analysis of a stationary source (or group of sources) of toxic pollutant(s) is performed to provide the most scientifically-refined indication of the impact of that source. This Tier involves the utilization of site-specific source and plant layouts as well as meteorological information. In contrast to the previous Tiers, Tier 3 allows for a more realistic simulation of intermittent sources and combined source impacts. In addition, results from short-term analyses indicate not only if a risk level of concern can be exceeded, but how often that level of concern might be exceeded during an average year. Dispersion modeling for the Tier 3 analysis procedure is based on use of EPA's Industrial Source Complex (ISC) model[18] and as such utilizes many of the same techniques recommended in the "Guideline on Air Quality Models (Revised)"[6] approach to the dispersion modeling of criteria pollutants.

To facilitate the dispersion modeling of toxic air pollutants, the EPA has developed TOXLT (TOXic modeling system Long-Term)[5] for refined long-term analyses, and TOXST (TOXic modeling system Short-Term)[4] for refined short-term analyses. The TOXLT system incorporates the ISCLT (long-term) directly to calculate annual concentrations and the TOXST system incorporates the ISCST (short-term) model directly to calculate hourly concentrations. Codes and user's guides for both TOXLT and TOXST are available via electronic bulletin board (see Appendix A).

4.2 Long-Term Modeling

Long-term Tier 3 modeling using the TOXLT[5] modeling system to estimate maximum annual concentrations and maximum cancer risks. The TOXLT modeling system uses the ISCLT model to calculate these annual concentrations at receptor sites which are specified by the user. A post-processor called RISK subsequently calculates lifetime cancer risks and chronic noncancer hazard index values at each receptor.

4.2.1 Maximum Annual Concentration Estimation

In addition to the information required to perform a Tier 2 long-term analysis, the Tier 3 long-term analysis requires the following information:

1. five years of meteorological data from the nearest National Weather Service (NWS) station. These data are for the most recent, readily-available consecutive five year period. NWS data are available through the electronic bulletin board (see Appendix A). Alternatively, one or more years of meteorological data from on-site measurements may be substituted. These data should be obtained and quality-assured using procedures consistent with the "Guideline on Air Quality Modeling (Revised)."[6]
2. plant layout information, including all emission point and fenceline locations. This information should be sufficiently detailed to allow the modeler to specify emission point and fenceline receptor locations within 2 meters.
3. pollutant-specific data concerning deposition or decay half-life, if applicable.

Once these data have been obtained, an input file should be prepared for execution of the ISCLT model using the guidance available in the ISC User's Guide.[18] The ISCLT model should then be executed using the TOXLT system. Procedures utilized should also be consistent with the TOXLT User's Guide[5] (available via electronic bulletin board, see Appendix A). Specific recommendations concerning the development of these inputs include:

1. Annual emission rates should be converted to g/s for input. The TOXLT modeling system uses "base emission rates" and "emission rate multipliers" to specify the emission rate for each pollutant/source combination. Thus, for a given pollutant and source the emission rate equals the base emission rate (specified in the ISCLT input file) times the emission rate multiplier for that pollutant/source combination (specified in the RISK input file). In general, the input file to the ISCLT program should specify the same emission rates used in previous modeling tiers for each source, and emission rate multipliers of 1.0 should then be provided as inputs to the RISK post-processor. (This doesn't necessarily have to be the case, as long as the product of the emission rate provided as input to ISCLT and the emission rate multiplier provided as input to RISK equals the actual emission rate being modeled for each source.) In the case where more than one pollutant is being emitted from the same source, that source should only be included once in the ISCLT input file, and emission rate multipliers should be provided to the RISK post-processor for each pollutant being emitted from that source.

2. In general, each source should be modeled as a single ISCLT source group. However, all sources of a single pollutant may be grouped into a single ISCLT source group. Each source of more than one pollutant should be modeled as a single ISCLT source group by itself.
3. Input switches to the ISCLT model should be set to allow the creation of the master file inventory for post-processing. The regulatory default mode should be used. Choose the printed output option for tabulating the greatest impacts of each source.
4. Stability Array (STAR) summaries of the NWS meteorological data should be created using the STAR program (this program and a description of its use are available on the electronic bulletin board, see Appendix A). These should be included in the input file according to the ISCLT User's Guide.
5. A polar or rectangular receptor grid may be used, but with sufficient detail to accurately estimate the highest concentrations. The design of the receptor network should consider the long-term results of the earlier modeling tiers such that the highest resolution of receptors is in the vicinity of the highest predicted impacts. Additional receptors may need to be added in sufficient detail to accurately resolve the highest concentrations.
6. Where appropriate, direction-specific building downwash dimensions should be included for each radial direction.

The printed ISCLT output will indicate the top 10 impacts for each source group, while the master file inventory will contain all of the annual concentration predictions from each source group at each receptor.

Continuing with the examples from Tiers 1 and 2, TOXLT was utilized to perform site-specific ISCLT dispersion modeling for the 4 stacks in the example. Each of the stacks was modeled as an individual source group. A STAR summary of five years of meteorological data from the nearest NWS site was utilized along with specific source and plant boundary locations according to Figure 1 below. Stacks are represented in the Figure as open circles, with stacks 3 and 4 located at the same place. A rectangular receptor grid (indicated by the filled circles) with 50m spacing outside the plant boundary was used to obtain concentration predictions. Neither pollutant was presumed to decompose in the atmosphere.

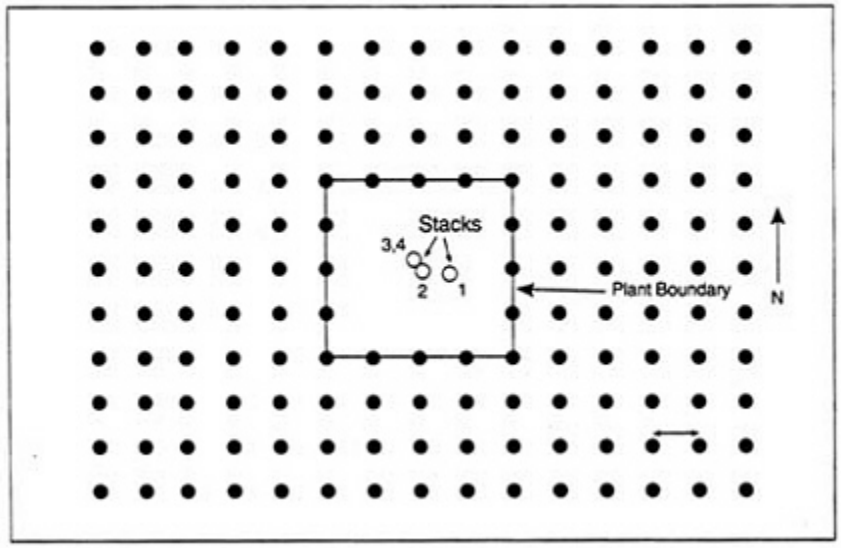

Figure 1. Schematic of Example Facility with Long-Term Impact Locations

The results of the dispersion modeling indicated the following maximum annual off-site concentrations for each of the source/pollutants combinations:

Source	Compound	Max. Impact	Location
Stack 1	Pollutant A	.788 μg/m^3	X
Stack 2	Pollutant A	.305 μg/m^3	Y
Stack 2	Pollutant B	.131 μg/m^3	Y
Stack 3	Pollutant B	.172 μg/m^3	Z
Stack 4	Pollutant B	.976 μg/m^3	Z

It should be noted that the maximum concentrations from each source/ receptor combination were not co-located. The positions of the maximum concentration from each source are indicated on Figure 1 corresponding to the letters X, Y, and Z in the table above. In general, the Tier 3 maximum concentration values are 25 to 30% as high as the Tier 2 values.

4.2.2 Cancer Risk Assessment

Concentrations from the ISCLT master file inventory are used by the RISK post-processor to calculate cancer risks at each receptor site in the ISCLT receptor array. RISK can then provide summaries of the calculated risks according to

user specifications. Use of the RISK post-processor requires the following considerations:

1. As stated above, emission rate multipliers for each pollutant from each source should be provided as inputs to the RISK post-processor such that the product of the base emission rate input to ISCLT and the emission rate multiplier input to RISK equals the emission rate being modeled.
2. Unit cancer risk factors are provided to RISK either in the RISK post-processor input file or through an interactive process in TOXLT.
3. The RISK post-processor output options should be exercised to provide the total cancer risk at each receptor due to all pollutants, as well as individual pollutant or source contribution to these receptor-specific risks.

If the maximum predicted lifetime cancer risk in the receptor grid is less than the designated level of concern (e.g., 1×10^{-6}), placement of additional receptors in the ISCLT receptor array should be considered as a means of ensuring that the simulation is not underestimating maximum risk. If the maximum cancer risk in the receptor array is greater than the designated level of concern, additional runs of the RISK post-processor may be performed using reduced emission rate multipliers to assess the impacts of possible emission control scenarios. If the analysis shows no cancer risk greater than the designated level of concern and the receptor array is deemed adequate, the modeled source is considered to be in compliance with the specified criterion. In the case of noncompliance, it may be desirable on the part of the modeler to conduct a more refined analysis. See Section 5.0 if this document discusses some of the possibilities for further modeling refinements.

The output of the Risk post-processor for the example plant indicates that the maximum lifetime cancer risk outside the plant boundary is 4.2×10^{-7}, located at point W on Figure 1. Such a result would indicate that the facility would not cause a significant cancer risk to the public, according to the cancer risk level specified by the CAAA of 1990.

4.2.3 Chronic Noncancer Risk Assessment

In this assessment, concentrations from the ISCLT master file inventory are used by the RISK post-processor to calculate chronic noncancer hazard index values for a specific noncancer effect at each receptor site in the ISCLT receptor array. RISK can then provide summaries of the calculated index values according to user specifications. A separate risk simulation should be performed for each chronic noncancer effect being considered. Use of the RISK post-processor requires the following considerations:

1. As stated above, emission rate multipliers for each pollutant from each source should be provided as inputs to the RISK post-processor such that the product of the emission rate input to ISCLT and the emission rate multiplier input to RISK equals the actual emission rate being modeled.
2. Chronic threshold concentration values for the specific noncancer effect are provided to RISK either in the RISK post-processor input file or through an interactive process in TOXLT.
3. The RISK post-processor output options should be exercised to provide the total noncancer hazard index at each receptor due to all pollutants, as well as individual pollutant or source contribution to these receptor-specific hazard indices.

If the maximum hazard index value in the receptor grid exceeds 1.0, emission reduction scenarios can be performed (again, using reduced emission rate multipliers) to determine how this hazard index value can be reduced below 1.0. If the maximum hazard index value in the receptor grid does not exceed 1.0, the source(s) being modeled is considered to be in compliance with the specified criteria. In the case of non-compliance, it may be desirable on the part of the modeler to conduct a more refined analysis. See Section 5.0 if this document discusses some of the possibilities for further modeling refinements.

Using the chronic noncancer threshold concentration values for pollutants A and B of 20.0 and 5.0 $\mu g/m^3$, respectively, the RISK post-processor was exercised for the example facility to obtain a maximum hazard index value of 0.27 located at point Z on Figure 1. This result, which is approximately 30% of the Tier 2 result, would indicate that the facility does not present significant chronic noncancer risk in its current configuration.

4.3 Short-term Modeling

Short-term Tier 3 modeling uses the TOXST modeling system[4] to estimate maximum hourly concentrations and the receptor-specific expected annual number of exceedances of short-term concentration thresholds. For multiple pollutant scenarios, this amounts to the number of times the acute hazard index value exceeds 1.0. The model uses the ISCST model to calculate these hourly concentrations at receptor sites which are specified by the user. Acute hazard index values are subsequently calculated at each receptor by the TOXX post-processor, in which a Monte Carlo simulation is performed for intermittent sources to assess the average number of times per year the acute hazard index value exceeds 1.0 at each receptor.

4.3.1 Maximum Hourly Concentration Estimation

In addition to the information required to perform a Tier 2 analysis, the Tier 3 short-term analysis requires the following information:

1. Five years of meteorological data from the nearest National Weather Service (NWS) station. These data are for the most recent, readily available consecutive five year period. NWS data are available through the electronic bulletin board (see Appendix A). Alternatively, one or more years of meteorological data from on-site measurements may be substituted. These data should be obtained and quality-assured using procedures consistent with the "Guideline on Air Quality Modeling (Revised)."[6]
2. plant layout information, including all emission point and fenceline locations. This information should be sufficiently detailed to allow the modeler to specify emission point and fenceline receptor locations within 2 meters of their actual locations.
3. pollutant-specific data concerning deposition or decay half-life, if applicable.
4. source-specific data concerning the annual average number of releases and their duration for all randomly-scheduled intermittent releases.

Once these data have been obtained, an input file should be prepared for execution of the ISCLT model using the guidance available in the ISC User's Guide.[18] The ISCST model should then be executed using the TOXST system. Procedures utilized should also be consistent with the TOXST User's Guide[5] (available through the electronic bulletin board, see Appendix A). Specific recommendations concerning the development of these inputs include:

1. Maximum hourly emissions rates are used for the analysis. The TOXST modeling system uses "base emission rates" and "emission rate multipliers" to specify the emission rate for each pollutant/source combination. Thus, for a given pollutant and source the emission rate equals the base emission rate (specified in the ISCST input file) times the emission rate multiplier for that pollutant/source combination (specified in the TOXX input file). The input file to the ISCST program should contain the same emission rates used in previous modeling tiers for each source, and the input file to the TOXX post-processor should be provided unit emission rate multipliers (1.0). If more than one pollutant is being emitted from the same source, that source may be included once in the ISCST input file with a unit emission rate (1.0) and the individual pollutant emission rates may be provided to the TOXX

post-processor. (It should be noted that this may complicate the interpretation of the printed ISCST output. Alternatively, multiple pollutants from the same source may be modeled as individual sources with actual emission rates in ISCST and unit emission rates in TOXX. This may require more computing time, but may allow direct interpretation of concentration predictions in the ISCST printed output. Regardless of which method is used, the modeler should take care that the product of the emission rate used in ISCST and the emission rate used in TOXX equals the emission rate of the pollutant and source being modeled.)

2. All continuous sources of the same pollutant should be modeled as one ISCST source group. Each intermittent source operating independently from one another should be modeled as a separate ISCST source group. All intermittent sources of the same pollutant emitting at the same tine may be modeled in the same ISCST source group. However, each source of more than one pollutant should be modelled as a source group by itself.
3. Input parameters in the ISCST input file should be set in accordance with the TOXST User's Guide. The regulatory default mode should be used. The ISCST output options should be chosen to provide summary results of the top 50 impacted receptors for each source group. (As noted earlier, if unit emission rates are being used in ISCST, interpretation of the concentration impacts as absolute may be inappropriate.)
4. Meteorological input files for ISCST may be created from NWS meteorological data using the RAMMET program (this program and a description of its use are available on the electronic bulletin board, see Appendix A).
5. A polar or rectangular receptor grid may be used, but with sufficient detail to accurately estimate the highest concentrations from each source. The design of the receptor network should consider the short-term results of the earlier modeling tiers such that the highest resolution of the receptors is in the vicinity of the highest predicted impacts. Additional receptors may need to be added in sufficient detail to accurately resolve the highest concentrations.
6. Where appropriate, direction-specific building downwash dimensions should be included for each radial direction.
7. The ISCST model option to create a TOXFILE output for post-processing should be chosen. The concentration threshold value (called "pcutoff") used to reduce the size of this binary concentration output file should be chosen appropriately to eliminate predicted concentration values below possible

concern. Although it may be set higher, a good rule of thumb for setting this value is:

$$pcutoff = \frac{LACT}{\sum_{i=1}^{a} (Npol)_i}$$

where *LACT* is the lowest acute concentration threshold value in the group of pollutants being modeled, and $Npol_i$ is the number of pollutants emitted from ISCST source group *i*.

The printed ISCST output will indicate the top 50 impacts for each ISCST source group, and the TOXFILE will contain all of the concentrations above the cutoff value from each ISCST source group at each receptor.

The ISCST model was exercised for the example facility. The maximum 1-hour concentrations for each source/pollutant combination were determined to be as follows:

Source	Compound	Max. Impact	Location
Stack 1	Pollutant A	34.5 μg/m^3	Q
Stack 2	Pollutant A	67.9 μg/m^3	R
Stack 2	Pollutant B	29.1 μg/m^3	R
Stack 3	Pollutant B	39.2 μg/m^3	S
Stack 4	Pollutant B	47.5 μg/m^3	S

The locations of the predicted maximum 1-hour concentrations are shown in Figure 2. The maximum impacts from each source were only slightly lower than those from the Tier 2 analysis.

4.3.2 Acute Hazard Index Exceedance Assessment

Concentrations from the ISCST master file inventory are used by the TOXX post-processor to calculate acute hazard index values for each hour of a multiple-year simulation period at each receptor site in the ISCST receptor array. The program then counts the number of times a hazard index value exceeds 1.0 (an exceedance) and prints out a summary report which indicates the average number of times per year an exceedance occurs at each receptor. The use of the TOXX post-processor requires the following considerations:

1. As stated above, in most cases unit emission rate multipliers for each pollutant from each source are used as inputs to the TOXX post-processor.

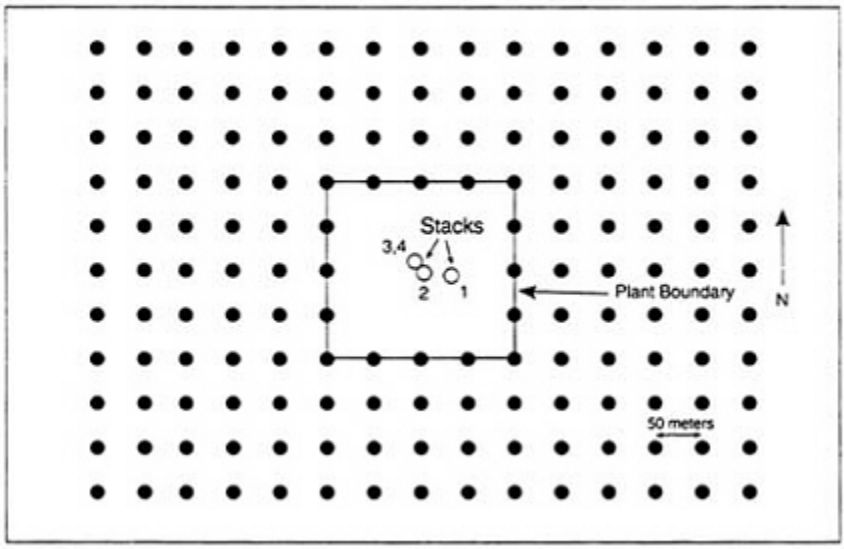

Figure 2. Schematic of Example Facility with Short-term Impact Locations

2. Acute threshold concentration values are provided to TOXX as the health effects thresholds in the TOXX post-processor input file.
3. The TOXX output option should be chosen to output the exceedances in polar grid format. Exceedance counts at discrete fenceline receptors will appear at the end of this table in the order in which discrete receptor locations were input to ISCST.
4. If only one pollutant is being modeled, the additive exceedance calculation option should not be chosen. If multiple pollutants are being modeled, the additive exceedance calculation option should be chosen. The TOXX post-processor should be set to perform 400 or more simulation years (maximum 1000). Unless otherwise specified by EPA guidance, background concentrations for toxic air pollutants should be set equal to 0.
5. The frequency of operation for each emission source is specified by providing values for the probability of the source switching on and the duration of the release. For each continuous emission, the probability of the source switching on is 1.0, and for each intermittent emission source, the probability of the source switching on is equal to the average number of releases per year divided by 8760 (the number of hours in a non-leap year).

The duration of release for each continuous source should be set equal to 1.0, and the duration of release for each intermittent release should be specified as the nearest integer hour which is not less than the release duration. (For example, if the average release duration is less than 1 hour, the duration of the release should be set equal to 1; if the average release duration is 3.2 hours, the duration of release should be set equal to 4.)

If the maximum number of acute hazard index exceedances in the receptor grid is less than some specified value (e.g., 0.1, equivalent to an average of 1 hourly exceedance every 10 years), the modeled source is considered to be in compliance with the acute threshold concentration criteria. However, resimulation with placement of additional receptors in the ISCST receptor array should be considered as a means of assuring that the simulation is not underestimating the maximum acute hazard index. If the maximum number of hazard index exceedances in the receptor array is greater than the specified value, additional runs of the TOXX post-processor with reduced emissions rate multipliers may be performed to assess the impacts of possible emission control scenarios. In the case of non-compliance, it may be desirable on the part of the modeler to conduct a more refined analysis. Section 5.0 of this document discusses such possibilities.

The TOXX post-processor was exercised for the example facility using the results form the ISCST simulation. The frequency of operation for each source ranged from 0.14 to 0.84, reflecting the actual yearly frequency of "on" time for each source. The output showed that none of the receptors experienced an impact resulting in a hazard index value of 1.0 or greater. Comparing this result with the Tier 2 result indicates that the hazard index never exceeds 1.0 because in a Tier 3 analysis the maximum impacts are seen not to occur at the same place and time. This indicates that the facility does not cause a significant health risk from acute exposure in its current configuration.

5.0 Additional Detailed Analyses

If any Tier 3 analyses indicate non-compliance with any of the user-specified criteria, it may be desirable to conduct an additional, more refined analysis. This may mean the use of on-site meteorological data or it may mean that a more appropriate modeling procedure is deemed applicable for the specific case. The determination of an appropriate alternative modeling procedure can only be made in a manner consistent with the approach outlined in the "Guideline on Air Quality Models (Revised)."[6]

In some cases, the EPA may allow exposure assessments to incorporate available information on actual locations of residences, potential residences, businesses, or population centers for the purpose of establishing the probability of human exposure to the predicted levels of toxic pollution near the source being modeled. In such cases, use of the Human Exposure Model (HEM II)[19] with the ISCLT dispersion model is preferred. Again, if the use of other modeling procedures is desired, the approval of a more appropriate alternative modeling procedure can only be made in a manner consistent with the approach outlined in Section 3.2 of the "Guideline on Air Quality Models (Revised)."[6]

6.0 Summary Of Differences Between Modeling Tiers

To summarize the major differences between the 3 modeling tiers described in this document, Table 3 below briefly lists the input requirements, output parameters, and assumptions associated with each tier. This Table may be used to quickly determine whether a given scenario may be modeled at any particular tier. Within each tier, cancer unit risk estimates, chronic noncancer concentration thresholds, and acute concentration thresholds are required to convert concentration predictions into cancer risks, chronic noncancer risks, and acute noncancer risks, respectively.

Modeling Tier	Input Requirements	Output Parameters	Major Assumptions
Tier 1	emission rate, stack height, minimum distance to fenceline	maximum off-site concentrations, worst-case cancer risk or worst-case noncancer hazard index (short- and long-term)	worst-case meteorology, worst-case downwash, worst-case stack parameters, short-term releases occur simultaneously, maximum impacts co-located, cancer and noncancer risks additive
Tier 2	emission rate, stack height, minimum distance to fenceline, stack velocity, stack temperature, stack diameter, rural/urban site classification, building dimensions for downwash calculations	maximum off-site concentrations, worst-case cancer risk and/or worst-case noncancer hazard index (short- and long-term)	worst-case meteorology, short-term releases occur simultaneously, maximum impacts co-located, cancer and non-cancer risks additive
Tier 3	emission rate, stack height, actual fenceline and release point locations, stack velocity, stack temperature, stack diameter, rural/urban site classification, local meteorological data, receptor locations for concentration predictions, frequency and duration of short-term (intermittent) releases	concentrations at each receptor point, long-term cancer risk estimates, chronic noncancer hazard index estimates at each receptor point, annual hazard index exceedance rate at each receptor.	cancer and noncancer risks additive

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Appendix A Electronic Bulletin Board Access Information

The Office of Air Quality Planning and Standards (OAQPS) of the EPA has developed an electronic bulletin board network to facilitate the exchange of information and technology associated with air pollution control. This network, entitled the OAQPS Technology Transfer Network (TTN), is comprised of individual bulletin boards that provide information on OAQPS organization, emission measurement methods, regulatory air quality models, emission estimation methods, Clean Air Act Amendments, training courses, and control technology methods. Additional bulletin boards will be implemented in the future.

The TTN service is free, except for the cost of the phone call, and may be accessed from any computer through the use of a modem and communications software. Anyone in the world wanting to exchange information about air pollution control can access the system, register as a system user, and obtain full access to all information areas on the network after a 1 day approval process. The system allows all users to peruse through information documents, download computer codes and user's guides, leave questions for others to answer, communicate with other users, leave requests for technical support from the OAQPS, or upload files for other users to access. The system is available 24 hours a day, 7 days a week, except for Monday, 8-12 a.m. EST, when the system is down for maintenance and backup.

The model codes and user's guides referred to in this document, in addition to the document itself, are all available on the TTN in the bulletin Board entitled SCRAM, short for Support Center for Regulatory Air Models. Procedures for downloading these codes and documents are also detailed in the SCRAM bulletin board.

Documentation on EPA-approved emission test methods is available on the TTN in the bulletin board entitled EMTIC, short for the Emission Measurement Testing Information Center. Procedures for reading or downloading these documents are also detailed in the EMTIC bulletin board.

The TTN may be accessed at the phone number (919)-541-5742, for users with 1200 or 2400 bps modems, or at the phone number (919)-541-1447, for users with a 9600 bps modem. The communications software should be configured with the following parameter settings: 8 data bits; 1 stop bit; and no (N) parity. Users will be asked to create their own case sensitive password, which they must remember to be able to access the network on future occasions. The entire network is menu-driven and extremely user-friendly, but any users requiring assistance may call the system operator at (919)-541-5384 during normal business hours EST.

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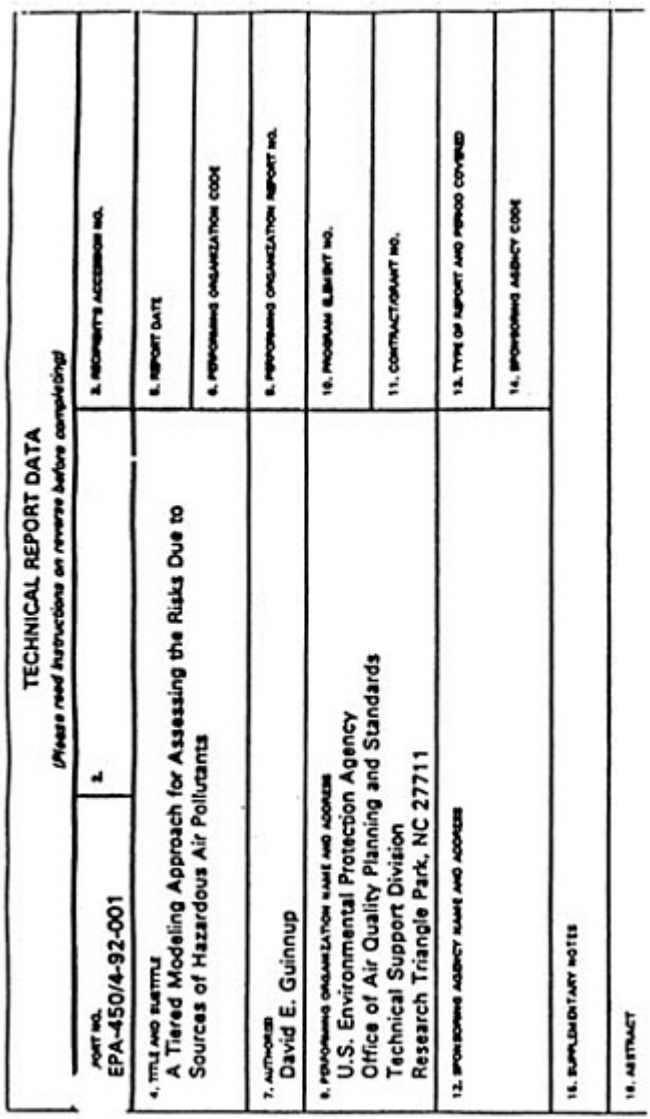

TECHNICAL REPORT DATA

(Please read instructions on reverse before completing)

1. REPORT NO. EPA-450/4-92-001	2.
3. RECIPIENT'S ACCESSION NO.	
4. TITLE AND SUBTITLE A Tiered Modeling Approach for Assessing the Risks Due to Sources of Hazardous Air Pollutants	5. REPORT DATE
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) David E. Guinnup	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS U.S. Environmental Protection Agency Office of Air Quality Planning and Standards Technical Support Division Research Triangle Park, NC 27711	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE
15. SUPPLEMENTARY NOTES	
16. ABSTRACT	

TECHNICAL REPORT DATA FORM

This document provides modeling guidance to support risk assessments as applied to stationary sources of hazardous air pollutants. The guidance focuses on procedures which may be used in support of the petition processes described in Title III of the Clean Air Act Amendments of 1990. The analysis approach described herein is a tiered one, in which each subsequent modeling tier requires additional site-specific information to produce a less conservative estimate of the risk associated with a given stationary source (or group of sources). The modeling approach begins with Tier 1 screening tables which require only source emission rates, stack heights, and nearest fenceline distances to estimate maximum cancer and/or noncancer risks. Tier 2 utilizes additional source parameters (including stack diameter, exit gas temperature and velocity, and nearby building dimensions) with the SCREEN computer program to develop more refined estimates of maximum risks. Tier 3 utilizes site-specific meteorological data, plant layout information, and release frequency data with the TOXST and TOXLT computer models to provide additional refinement to these assessments.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Air Pollution Atmospheric Dispersion Modeling Risk Assessment		

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
Release Unlimited	Unclassified	
	20. SECURITY CLASS (This Page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

Appendix K

Science Advisory Board Memorandum on the Integrated Risk Information System and EPA Response

Honorable William K. Kelly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W. Washington, D.C. 20460

Subject: Science Advisory Board's review of the Integrated Risk Information Systems

Dear Mr. Reilly:

The Environmental Health Committee of the Science Advisory Board (SAB) was given a presentation by EPA staff on the Integrated Risk Information System (IRIS) at its meeting on October 26, 1989. The presentation also included discussion of the activities of the Carcinogen Risk Assessment Verification Endeavor (CRAVE) and the RfD (Reference Dose) Review Group.

While it is our understanding that the IRIS was developed primarily for use within EPA, the Committee believes that the IRIS would be of great utility both within EPA and other organizations concerned with the potential health impacts of toxic chemicals in the environment. IRIS has the potential to provide a summary of toxicological data for a large number of chemicals in readily accessible form, either from an EPA on-line computer data bank, from access through existing routes such as the National Library of Medicine's TOXNET, or from

regularly updated computer diskettes distributed to IRIS users. Many state and local regulatory agencies, as well as scientists working in the field of regulatory toxicology, would find IRIS to be a valuable reference source.

The IRIS files contain not only the toxicological data, but also EPA's summary of these data, which may be in the form of the weight-of-evidence characterization for carcinogenicity, unit risk numbers for substances judged to have sufficient evidence for carcinogenicity in animals or humans, and reference dose numbers. This type of information may be widely used both within EPA and by other environmental regulatory agencies as the basis for regulatory decisions. It is therefore very important that the information in IRIS be carefully reviewed for its accuracy, timeliness, and completeness, and that appropriate caveats regarding the data and EPA's evaluation of the data be included in the IRIS files.

We recommend that SAB reviews of Agency documents on specific substances be referenced in the IRIS files for these substances. A short summary of the SAB evaluation of EPA conclusions, especially as to the weight-of-evidence characterization, unit risk, or reference dose, should also be included in the IRIS file, and a short summary of any subsequent communication from the Administrator back to SAB in response to its evaluation.

We understand that Federal Register notices of proposed regulatory actions and final regulatory actions for chemicals in IRIS are now included in the regulatory summaries of IRIS files for those chemicals, a step forward which we commend. In the same vein, major EPA scientific reports such as health advisories, health assessment documents, criteria documents, and Risk Assessment Forum reports should also be cited in IRIS files, and we understand that this will occur in the future. Checks of the files for individual chemicals indicated that IRIS currently lacks citations to some key EPA reports on specific chemicals.

The current computer implementation of IRIS is somewhat cumbersome. For example, capabilities such as returning to earlier text in files or doing searches for specific words or phrases are not available in the current implementation. We understand that the computer implementation of IRIS will be upgraded, and we urge EPA to develop an implementation that is flexible, and "user friendly" for the spectrum of anticipated users both inside and outside of EPA. EPA should also consider the need for, and potential benefits from, developing more training materials and on-line help capabilities to assist users unfamiliar with IRIS to learn how to use the system. In any such efforts, EPA should remain cognizant that an increase in users should be expected, and the system designed accordingly.

The Agency needs an overall strategy on computerized lists of chemicals,

one which takes into account the differing needs of various segments of the user community. While IRIS may be vary helpful for those wishing to know about the toxicological data, other users may simply wish to know what regulatory actions EPA has taken on a specific chemical, or how to deal with an emergency response in the event of chemical spills. EPA either has or is developing other computerized lists of chemicals, but the planning and coordination among these efforts could be improved. EPA should consider what computerized chemical lists are needed, and, more broadly, how modern computer and telecommunications technology can assist in the processes of risk assessment and risk management for the thousands of chemicals that are of interest to EPA. The Agency should then take steps to assure coordination, cross referencing, and standardization in access procedures for the various computerized lists of chemicals it is, and will be, developing.

The Environmental Health Committee is pleased to have had the opportunity to review IRIS and to offer its advice. We would appreciate your response to the major points we have raised:

1. Need for critical review of data for accuracy and completeness
2. Inclusion of SAB evaluation
3. Citation of major relevant EPA reports, including health advisories and other key documents
4. Implementation of improved electronic systems to allow more flexible handling of the data
5. Development of training materials and on-line help
6. Coordination, cross-referencing, and standardization of access to the various listings under development.

We will be pleased to assist the Agency further as it proceeds with the development of IRIS and other computerized chemical lists.

Dr. Raymond Loehr, Chairman
Science Advisory Board Executive Committee
Dr. Arthur Upton, Chairman
Environmental Health Committee

Dr. Raymond Loehr
Chairman
Science Advisory Board
U.S. Environmental Protection Agency
401 M Street, S.W. Washington, D.C. 20460

Dear Ray:

Thank you very much for your letter of March 14, 1990, and your comments on the Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS). I greatly appreciate, and share, the Science Advisory Board's interest in IRIS and its future.

As you correctly state, IRIS is an important risk information resource both for the Agency, and for other organizations concerned with the potential health impacts of toxic chemicals in the environment. Because the summary risk information on, to date, 397 chemicals represents authoritative EPA consensus positions on the adverse health effects of these chemicals, the Agency is aware of its obligation to the user community to provide system oversight and quality assurance. I share your concerns that the IRIS risk information be as accurate, timely, and complete as possible, and that appropriate discussion and/or caveats be included in the IRIS files.

In your letter you raise several interesting points which I have asked the Office of Health and Environmental Assessment in the Office of Research and Development, responsible for IRIS development and management, to reply. Please see the enclosure for a detailed response.

Again, thank you very much for your letter and your interest in the Agency's IRIS data base. We welcome your comments and appreciate your offer to work with the Agency as it proceeds with future development of IRIS.

Sincerely yours,
William K. Reilly

Enclosure

The Integrated Risk Information System (IRIS) is one of the Agency's major risk information resource tools containing summaries of health risks and EPA regulatory information on, to date, 397 chemicals. Updated monthly, it is used by EPA to provide high quality, timely scientific and technical information to Agency scientists, and promote Agency-wide coordination and consistency of risk assessments. Because IRIS, containing authoritative consensus EPA positions on chemical-specific potential adverse health effects, is used extensively both inside and outside the Agency, we recognize the need to maintain, and improve, the quality of the system, its access and delivery systems, and sufficient oversight. We welcome the Science Advisory Board's (SAB) interest and comments on IRIS and take this opportunity to respond to the major points raised in your March 14 letter.

1. **Data Review** - As you know, two Agency work groups develop the risk information summaries that appear in IRIS. Each work group is comprised of approximately 20 senior Agency scientists and statisticans from risk assessing program offices, laboratory facilities, and regional offices. During, and subsequent to, the work group deliberations, there are several levels of quality control and internal review built into the IRIS information development process. First, particularly in the case of the Carcinogenic Risk Assessment Verification Endeavor (CRAVE), an emphasis is placed on the use of external/ and or SAB peer-reviewed documents (e.g., Health Assessment Documents, Drinking Water Criteria Documents) to support these summaries and the quantitative risk values they contain. While the Reference Dose (RfD) Work Group process is different, actually developing the oral RfDs for each chemical, they use the same consensus procedures as the CRAVE Work Group. Also, the Oral RfD Work Group methodology has been peer-reviewed and receives SAB oversight.

Second, an extensive technical quality control process is part of each work group's operating procedures. Technical quality control includes internal work group draft Summary review, final Summary review, final check prior to IRIS loading, and a further check after the summary is online. This final consensus summary sheet development is the primary goal of the work groups and reflects the diligence and hard work of the group Chairs and members.

Third, an editorial quality check is conducted prior to loading on the System. This check, performed by a contractor, is being done on all chemical files currently on IRIS and on new files before they go online. It includes an edit for clarity, style, continuity, and typographical errors.

Finally, since 1986 when IRIS was made available to the Agency, and 1988 when IRIS was made available to the public, its use has grown far beyond earlier expectations. We acknowledge that additional oversight of the system is warranted.

To that end, EPA's Risk Assessment Council, which is chaired by Deputy Administrator F. Henry Habicht II, has established a subcommittee for IRIS. This subcommittee, chaired by Dr. William H. Farland, Director, Office of Health and Environmental Assessment, Office of Research and Development, will address both generic and chemical-specific issues concerning IRIS and its associated work groups. Also, IRIS status will be an agenda item at each Council meeting.

These various levels of review and oversight help to assure that IRIS remains an important resource toll and that the quality and validity of the information continues to improve.

2. **SAB Evaluations** - Preliminary discussions with SAB Director Dr. Donald Barns regarding addition to IRIS of short summaries that could include SAB evaluation of and comments on the principal EPA documents that support the CRAVE and RfD findings, have taken place. The inclusion of the SAB information would underscore the argument that while individual IRIS summaries are not peer-reviewed, the reports and documents on which the summaries are based have received external review. The process and management details on how to accomplish this task will be worked out in conference with Dr. Barnes, Dr. Farland, and the IRIS staff.

3. **EPA Reports** - Only citations for EPA scientific reports and other references used in developing the RfD and/or CRAVE summaries are included in IRIS. Full bibliographies listing those references are currently being prepared and loaded on the System. Thus far, bibliographies for 251 chemicals are online, with 146 to go. Once the addition of all bibliographies are complete, a user will have citations for all reports, studies, and documents used by the two work groups. Also, summaries of Drinking Water Health Advisories are included on IRIS in Section III: HEALTH HAZARD ASSESSMENT FOR VARIED EXPOSURE DURATIONS. A backlog of the Drinking Water summaries currently exists. The IRIS staff is in the process of putting them on the system.

When IRIS was initially developed in 1986, EPA Regulatory Actions (Section IV) were part of the system. These regulatory action sections provide information, including applicable Federal Register citations, for the Clean Air Act, Safe Drinking Water Act, Clean Water Act, Federal Insecticide, Rodenticide and Fungicide Act, Toxic Substances Control Act, Resource Conservation and Recovery Act and the Superfund Reauthorization Act. Because this regulatory information is subject to change, we are aware that this section needs to be carefully reexamined to insure that it is up-to-date and complete. Working with the Risk Assessment Council's IRIS Subcommittee, the IRIS staff is in the process

of developing a proposal to review and update the present regulatory action section. This work should commence in the near future.

4. **Delivery Systems** - Currently, Agency scientists and SAB members access IRIS using the EPA Electronic Mail system (EMAIL). IRIS on EMAIL is slow, cumbersome, and offers little or not reporting capabilities. In 1986, IRIS was a new Agency resource tool containing both qualitative and quantitative risk assessment information. The EMAIL delivery system, by design, obliged users to look at the whole chemical file, not just selected small sections, thus providing a wider chemical profile. At that time, there was concern that only the quantitative risk values would be accessed and not the qualitative discussion of the underlying studies, reports, assumptions, and limitations which is critical in evaluating and understanding the derivation of the risk values. As risk assessment methodologies have become more sophisticated, so too have IRIS users become more experienced and sophisticated in interpreting, evaluating, and using the IRIS risk information. Therefore, the time is right to provide them with a greatly enhanced delivery system that is fast, flexible, interactive, and user friendly.

On March 5, 1990, IRIS became available on the National Library of Medicine's (NLM) Toxicology Network (TOXNET). TOXNET is an online system that is highly regarded and easily accessed. IRIS on TOXNET provides many of the sophisticated functions requested by users. For more information on TOXNET, please refer to the enclosed NLM IRIS Fact Sheet.

Also, a Personal Computer (PC) based version of IRIS is being developed. The PC delivery system will provide the user with sophisticated user capabilities including easy movement within files, reliable keyword and string searches, reporting options, and a fast, accurate, and easily accessible system. We anticipate its availability in early 1991.

5. **Training Materials** - Your comments on the need for more and better developed IRIS training materials and online help are correct. The current user guide was inadequate for the users needs and did not provide clear, concise, and complete instructions. A revised user guide has been completed and the final version will be available both online and in paper copy by the end of May 1990. Also, development of new online help and other training materials are under consideration, including a revised case study, fact sheets, and interactive demonstration diskettes.

Training has been an important part of IRIS from its inception. A large training program both at Headquarters and in the Regions accompanied IRIS's availability in 1986. Presently, each Region has its own IRIS coordinator who

conducts training as needed, and the IRIS staff conducts workshops and seminars both inside and outside the Agency on a regular basis. A joint symposium, sponsored by EPA and the Chemical Manufacturers Association, on IRIS and some of its underlying risk assessment methodologies is being considered as another opportunity to stress appropriate use of the system. Also, finalization and distribution of the PC version of IRIS will result in another round of intensive Agency-wide user training.

6. **List Coordination** - The Agency recently took a major step forward in coordinating and cross-referencing regulatory and regulation-like lists, by approving development of a pointer system that will contain references to all chemicals and other pollutants regulated by EPA and to all the lists on which each chemical or pollutant occurs. This system, tentatively called the Registry of Lists, is currently under development; a prototype should be built during this calendar year, and the system should be generally available in one to two years. It will be designed as a pointer system, telling users where other information is available, because each individual list has been compiled for different programmatic reasons, and there is generally not a uniform set of data elements across the lists. IRIS chemicals will be referred to explicitly in the Registry of Lists, and IRIS and the Registry will be compatible to ensure that IRIS users can get complete cross-reference information.

If you have further questions or comments regarding any of the responses included above, please contact Linda Tuxen, EPA IRIS Coordinator, at 202-382-5949 (FTS 382-5949).

Appendix L

Development of Data Used in Risk Assessment

This appendix provides additional information on the data needed to estimate different elements in the risk-characterization steps of emission characterization, transport and fate, exposure assessment, and assessment of toxicity.

Emission Characterization

The best approach to characterizing emissions is to measure the flux from each manufacturing, storage, use, or disposal facility. However, such flux measurements are generally not available, because sources are not uniform across geography or time, because they are so large (e.g., a several-square-block manufacturing site) that no point for measuring flux is apparent, or because flux measurements are so difficult and expensive, and require such detailed knowledge of local meteorology, as to be impractical. Therefore, most emission data are calculated or estimated from industry-wide averages applied to such things as "emission factors," process rates, quantities of chemical present at given locations, or numbers of individual components. Some information that might be needed to estimate and characterize emissions from a facility is provided in Table L-1. (Not all information is needed for all calculation methods.)

Transport And Fate

Atmospheric-chemistry models are used to determine where emitted chemicals are transported and their characteristics when deposited. Several kinds of information are needed to estimate the transport and fate of pollutants:

TABLE L-1 Potential Data Needs for Calculation of Emissions

Process Vents

1. Volumetric flow rate of vent gas
2. Vent-gas discharge temperature
3. Concentration of individual or aggregate HAP
4. Operating hours per year of unit operation
5. Molecular weight of gas
6. Efficiency of control device
7. Production rate during measurement

Fugitive Emission

1. Numbers of pumps, valves, flanges, pressure-relief valves, open-ended lines, and compressors
2. Screening level
3. Weight % of HAPS in stream
4. Percent leaking equipment
5. Other HAPS characterization
6. Frequency of leak checking

Loading Emission

1. Type of cargo carrier
2. Mode of operation
3. Annual volume of liquid loaded
4. Temperature of liquid loaded
5. Weight in percent of HAP in loaded material
6. True vapor pressure of HAP loaded
7. Molecular weight of HAP
8. Efficiency of control device

Storage-Tank Emissions

1. Material stored
2. Diameter of tank
3. Rim seal type
4. Tank, roof, and shell color
5. Ambient temperature
6. Wind speed
7. Density and partial pressure of chemical
8. Molecular weight
9. Vapor pressure
10. Efficiency of control device
11. Type of storage tank
12. Annual throughput
13. Number and diameter of columns

Emission Factors

1. Magnitude of input into the process
2. Production level

Wastewater Sources

1. Volumetric flow rate of wastewater
2. Concentration
3. Production rate during flow determination
4. Production rate during concentration determination

Source: EPA, 1991c.

- Data on emissions of pollutants that result from production, storage, use, and disposal (discussed in previous section).
- Data on physical and chemical properties of pollutants (see Table L-2). For example, the vapor pressure of a chemical pollutant plays a major role in determining exchange of the chemical between the atmosphere and other environmental media. The vapor pressures of chemicals vary widely from those of gases (such as CO, CO_2, and SO_2), with vapor pressures of more than 1 atm, to those of aromatic compounds, organophosphates, dioxins, and other non-criteria pollutants, which are often in the range of 10^{-8}-10^{-3} atm. VOCs generally have vapor pressures of greater than 10^{-3} atm and semivolatile compounds vapor pressures of 10^{-8}-10^{-3} atm. Lead and other inorganic species are volatile as well. Water solubility's important, because, with vapor pressure, it determines the distribution of a pollutant in the atmosphere. Water-soluble vapors, for example, might be efficiently scrubbed from air by rainfall or fog deposition—processes that can minimize human exposure, at least by inhalation. Suspended dust or aerosol particles can adsorb vapors of the pollutant and may also play a major role in determining the rate of exchange of chemicals between the atmosphere and other environmental media.
- Data on transformation, degradation, and sequestration of pollutants in the environment (Table L-2), including chemical, biologic, and physical data:

  — Chemical data (e.g., for atmospheric oxidation and photochemical reactions). Chemical breakdown depends on molecular structure, and for some substances breakdown is rapid. If the chemical is susceptible to nucleophilic attack, oxidation, or hydroxylation, alterations can occur rapidly and change the potential exposure dramatically.

  — Biologic data (e.g., on degradation by metabolic action of microorganisms). Alterations by biologically mediated reactions are enormously variable, and data are needed on products of alteration; for example, do emissions tend to become more toxic or less toxic?

  — Physical data (e.g., on solubility and gravitational settlement). For particles, gravitational settlement or sedimentation increases with the aerodynamic diameter of the particle. Physical processes that occur in the atmosphere can affect particle-removal efficiency. Hydroscopic particles can increase in size because of the accumulation of water from the vapor phase in the atmosphere; this growth can help in their removal by sedimentation and washout.
- Data on rate of removal of pollutants by various routes. For example, the rate of catalytic oxidation of SO_2 decreases if the water concentration in the atmosphere falls below that necessary to maintain catalyst droplets. The critical point seems to be the percent relative humidity; above this, rates of catalytic oxidation increase dramatically. In clean air, SO_2 emissions are only very slowly oxidized via homogeneous reactions of the gas phase to SO_2 vapor. The development of the kind of information described here is important for the prediction

TABLE L-2 Physicochemical Properties of Chemical and Its Atmospheric Environment Important in Transport-Fate Calculations

Properties of Chemical	Properties of Environment
Physical properties:	Particulate load:
Molecular weight	For dust, other solid particulate matter
Density	For liquid aerosols
Vapor pressure (or boiling point)	Oxidant level
Water solubility	Temperature
Henry's constant (air-water distribution coefficient)	Relative humidity
Lipid solubility (or octanol-water distribution coefficient)	Amount and intensity of sunlight
	Amount and frequency of precipitation
Soil sorption constant	Meteorologic characteristics:
Chemical properties:	Ventilation
Rate constants for	Inversion
Oxidation	Surface cover:
Hydrolysis	Water
Photolysis	Vegetation
Microbial decomposition	Soil type
Other modes of decomposition	
Particle properties:	
Size	
Surface area	
Chemical composition	
Solubility	

of risk associated with environmental pollutants. Such data could be used to identify the most probable routes through the environment and provide clues to the rate of degradation (alteration) from source to receptor. Knowing the probable routes and sinks, one can identify populations that should have special attention in an evaluation of potential health effects. More refined approaches might include selecting or developing models to estimate transport and fate of pollutants.

- Data on types of models to predict the persistence, transport, and fate of pollutants, including their input requirements, degree of accuracy and precision, and method of validation. Several models of aerial dissipation have been reported.

Exposure Assessment

To evaluate human exposure for risk-assessment purposes, information is needed on the following:

- Contaminants (e.g., types, in which media, at what concentrations, and for what durations).

- Exposed population (e.g., who is at risk, where, and under what circumstances; how long they are exposed and to what degree; and their intake of the contaminant from air, food, water, or through other relevant routes).

These are described in more depth below.

For the contaminant, the minimum data need include measured or estimated concentrations at the point of human contact for a specified duration. For air, concentration data are generated by sampling air and simultaneously or sequentially measuring the toxicant trapped at a given air flow rate and for a given period monitored. Beyond those generalities, analytical methods vary widely in specifics and in the key dimensions of accuracy (agreement with true value), precision (spread in data), and limit of detection. Errors can be large, particularly in trace analysis, so concerns are warranted about the quality of concentration data used in risk assessments. The following cautions are pertinent:

- all data should be collected with validated methods under strict quality-assurance and quality-control standards.
- A clear statement of uncertainty is fundamental to all analytic reports (Keith et al., 1983). Errors are likely to be greater with airborne trace-amount toxicants than with "criteria pollutants," which tend to occur at much higher concentrations. This is because the relative accuracy of instruments often decreases at low concentrations.
- A contaminant might be present but below the detection limit of the equipment. In this case, the concentration of the contaminant should not be assumed to be zero. Rather, the detection limit (or some agreed-on fraction of it) should be used in the processing of data.
- Vapors must be discriminated from particle-bound residues in air monitoring, especially for toxicants of low to intermediate vapor pressure.
- Data on trace toxicants should be confirmed by mass spectrometry or other confirmatory method to increase confidence in the results.

For the *exposed population*, the nature of the harm must be defined. It is important to assess the various degrees of exposure and the numbers within each identifiable set of the population, such as sets defined by age or health status. In the absence of personal monitoring data, geographic, behavioral (e.g., activity-pattern), and demographic considerations will often allow estimation of the exposure, although the estimated exposure might not be directly related to an individual's exposure.

Because exposure to a specific chemical is rarely confined to a single route (although one route might dominate), the total exposure must be calculated by summing air (inhalation), dermal, and dietary (food and water) intakes. For example, pollutants that begin as "air pollutants" can generate substantial exposures through other media if they can move from air to water, soil, or vegetation.

A case in point is that of chlorinated hydrocarbons (polychlorinated biphenyls, toxaphene, DDT, etc.) in the Arctic; the mechanism was long-range transport in the air, but the exposure of indigenous peoples in the region is through the diet and results from the uptake of chemicals deposited in the food chain.

Assessment Of Toxicity

A risk analysis must include an assessment of the toxicity of a chemical, i.e., of the potential hazard the public health. Such analysis can be based on a combination of experimental toxicity and human data. Clearly, information on the incidence of disease associated with known exposures to toxicants is the most useful for human risk assessment. It is also the least available, however, because it depends on the occurrence of some unplanned or unforeseen event (e.g., an accident or malfunction in a manufacturing facility) or it is collected for a narrowly defined population (e.g., a workforce) exposed at magnitudes and for durations well beyond what the general population experiences. For ethical (and also sometimes legal) reasons, controlled dose-response studies in humans are rare.

The human data that might be available for risk assessment are in three broad categories:

- *Clinical*. Outcome and disease data are reported for members of the general population, including, if known:
  - — A description of the outcome(s).
  - — The diagnostic criteria used.
  - — A description of individual characteristics that might affect outcomes (age, pre-existing illness, etc.).
  - — Exposure history, including dose and time frames.

The opinions of medical experts on the findings and the applicability of the results to the general population are also important in determining the usefulness of clinical evidence for risk assessment.

- *Toxicologic*. Outcome and disease data are reported for persons (usually volunteers, not members of the general population) after exposure under controlled experimental conditions, including:
  - — Description of the hypotheses tested.
  - — The criteria used to select the study groups.
  - — The relevance of the outcomes to the general population or specified subpopulations (e.g., potential high-risk groups).
  - — The diagnostic and detection methods.
  - — The experimental conditions.

— Personal characteristics that might affect exposure and outcome (e.g., age, sex, and pre-existing conditions).

In addition, the method of exposure (nature and composition of toxic agent, routes of exposure, media and means of exposure, time of exposure, and doses) and statistical evaluation (e.g., point and range estimates, measures of association and significance, and dose-response and time-response relations) should be described.

- *Epidemiologic*. Outcome and disease data are collected on groups of people in real-world settings. These data should be accompanied by:

— A description of the hypotheses tested.
— Criteria applied to select groups observed.
— Study methods and target-group participation rates.
— Diagnostic criteria for clearly defined outcomes.
— Exposure history and characteristics, including period and doses relevant to outcome studied.
— Evaluation of characteristics that might affect exposure and outcome (e.g., age, employment, activity patterns, and pre-existing health conditions).
— Appropriate statistical analyses of comprehensive outcome measures (e.g., point and range estimates, dose-response data, time-response analysis, and measures of association and significance)
— Interpretation of the findings, including analysis of generalizability, bias, and other confounding issues.

References

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Appendix M

Charge to the Committee

The charge to the committee, as stated in Section 112(o) of the Clean Air Act Amendments of 1990 (CAAA-90), is as follows:

(1) REQUEST OF THE ACADEMY.—Within 3 months of the date of enactment of the Clean Air Act Amendments of 1990, the Administrator shall enter into appropriate arrangements with the National Academy of Sciences to conduct a review of—

(A) risk assessment methodology used by the Environmental Protection Agency to determine the carcinogenic risk associated with exposure to hazardous air pollutants from source categories and subcategories subject to the requirements of this section; and

(B) improvements in such methodology.

(2) ELEMENTS TO BE STUDIED.—In conducting such review, the National Academy of Sciences should consider, but not be limited to, the following—

(A) the techniques used for estimating and describing the carcinogenic potency to humans of hazardous air pollutants; and

(B) the techniques used for estimating exposure to hazardous air pollutants (for hypothetical and actual maximally exposed individuals as well as other exposed individuals).

(3) OTHER HEALTH EFFECTS OF CONCERN.—To the extent practical, the Academy shall evaluate and report on the methodology for assessing the risk of adverse human health effects other than cancer for which safe thresholds

of exposure may not exist, including, but not limited to, inheritable genetic mutations, birth defects, and reproductive dysfunctions.

(4) REPORT.—A report on the results of such review shall be submitted to the Senate Committee on Environmental and Public Works, the House Committee on Energy and Commerce, the Risk Assessment and Management Commission established by section 303 of the Clean Air Act Amendments of 1990 and the Administrator not later than 30 months after the date of enactment [May 15, 1993] of the Clean Air Act Amendments of 1990.

(5) ASSISTANCE.—The Administrator shall assist the Academy in gathering any information the Academy deems necessary to carry out this subsection. The Administrator may use any authority under this Act to obtain information from any person and to require any person to conduct tests, keep and produce records, and make reports respecting research or other activities conducted by such person as necessary to carry out this subsection.

(6) AUTHORIZATION.—Of the funds authorized to be appropriated to the Administrator by this Act, such amounts as are required shall be available to carry out this subsection.

(7) GUIDELINES FOR CARCINOGENIC RISK ASSESSMENT.—The Administrator shall consider, but need not adopt, the recommendations contained in the report of the National Academy of Sciences prepared pursuant to this subsection and the views of the Science Advisory Board, with respect to such report. Prior to the promulgation of any standards under subsection (f), and after notice and opportunity for comment, the Administrator shall publish revised Guidelines for Carcinogenic Risk Assessment or a detailed explanation of the reasons that any recommendations contained in the report of the National Academy of Sciences will not be implemented. The publication of such revised Guidelines shall be a final Agency action for purposes of section 307.

Appendix N-1

The Case for "Plausible Conservatism" in Choosing and Altering Defaults

Adam M. Finkel

This Appendix was written by one member of our committee, who was asked to represent the viewpoint of those members of the committee who believe that EPA should choose and refine its default assumptions by continually evaluating them against two equally important standards: whether the assumption is scientifically plausible, and whether it is "conservative" and thus tends to safeguard public health in the face of scientific uncertainty. Indeed, these three themes of plausibility, uncertainty, and conservatism form most of the framework for the last six chapters of the CAPRA report, as reflected in the "cross-cutting" chapters on model evaluation, uncertainty and variability, and on implementing an iterative risk assessment/management strategy. The particular way these themes should come together in the selection and modification of default assumptions is controversial; hence, the remainder of this appendix is organized into five parts: (1) a general discussion of what "conservatism" does and does not entail; (2) an enumeration of reasons why conservatism is appropriately part of the rationale for choosing and departing from defaults; (3) the specific plan proposed for EPA's consideration;[1] (4) a side-by-side analysis of this proposal against the competing principle of "maximum use of scientific information" (see Appendix N-2 following this paper); and (5) general conclusions.

[1] Although I will discuss and evaluate the general issue of conservatism in detail before I present our specific recommendations, I urge readers to consider whether the proposal detailed in this third section bears any resemblance to the kind of "conservatism for conservatism's sake" that critics decry.

What Is "Conservatism"?

The most controversial aspect of this proposal within the full committee was its emphasis on "conservatism" as one—not the only—organizing principle to judge—not to prejudge—the merits of defaults and their alternatives. Supporters of this proposal are well aware that there are strengths and weaknesses of the conservative orientation that make it one of the most hotly-contested topics in all of environmental policy analysis, but also believe that few topics have been surrounded by as much confusion and misinformation. Some observers of risk assessment appear to be convinced that EPA and other agencies have so overemphasized the principle of conservatism as to make most risk estimates alarmingly false and meaningless; others, including at least one member of this committee, have instead suggested that if anything, the claims of these critics tend to be more reflexive, undocumented by evidence, and exaggerated than are EPA's risk estimates themselves (Finkel, 1989). It is clear that partisans cannot agree on either the descriptive matter of whether risk assessment is too conservative or on the normative matter of how much conservatism (perhaps any at all) would constitute an excess thereof. However, at least some of the intensity marking this debate is due to a variety of misimpressions about what conservatism is and what its ramifications are. Before laying out the proposal, therefore, some of these definitional matters will be discussed.

First, a useful definition of conservatism should help clarify it in the face of the disparate charges leveled against it. *Conservatism is, foremost, one of several ways to generate risk estimates that allow risk management decisions to be made under conditions of uncertainty and variability*. Simply put, a risk assessment policy that ignored or rejected conservatism would strive to always represent risks by their "true values" irrespective of uncertainty (or variability), whereas any attempt to consider adding (or removing) some measure of conservatism would lead the assessor to confront the uncertainty. Incorporating "conservatism" merely means that from out of the uncertainty and/or variability, the assessor would deliberately choose an estimate that he believes is more likely to overestimate than to underestimate the risk.

Rationality in managing risks (as in any endeavor of private or social decision making) involves the attempt to maximize the benefit derived from choice under specific conditions in the world. If we do not know those conditions (uncertainty) or do not know to whom these conditions apply (human interindividual variability), we have to make the choice that *would* be optimal for a *particular* set of conditions and essentially hope for the best. If the true risk we are trying to manage is larger or smaller than we think it is (or if there are individuals for whom this is so) then our choice may be flawed, but we still have to choose. Unlike the search for scientific truth, where the "correct" action in the face of uncertainty is to reserve one's judgment, in managing risks decisions are inevitable, since reserving judgment is exactly equivalent to making the judgment

that the *status quo* represents a desirable balance of economic costs expended (if any) and health risks remaining (if any). It is therefore vital that the risk assessment process handle uncertainties in a predictable way that is scientifically defensible, consistent with the Agency's statutory and public missions, and responsive to the needs of decision makers. Conservatism is a specific response to uncertainty that favors one type of error (overestimation) over its converse, but (especially if EPA follows the detailed prescriptions here) the fact that it admits that either type of error is possible is more important than the precise calculus it may use to balance those errors.

It is also crucial to understand what this asymmetry in favor of overestimation does and does not mean. Conservatism is *not* about valuing human lives above the money spent to comply with risk management decisions. Instead, it acknowledges that if there was no uncertainty in risk, society could "optimally" decide to spend a dollar or a billion dollars to save each life involved—conservatism is silent about this judgment. Assuming that society decides how it wishes to balance lives and dollars, conservatism only affects the decision at the margin, by deliberately preferring, from among the inevitable errors that uncertainty creates, to favor those errors which lead to *relatively* more dollars spent for the lives saved than those which lead to *relatively* fewer lives saved for the dollars spent.

Some would call this an orientation disposed to being "better safe than sorry" or a tendency towards "prudence," characterizations we do not dispute or shrink from. It is simply a matter of "good science" to admit that the true value of risk is surrounded by uncertainty, and that as a consequence, errors of overestimation or underestimation can still occur for whatever value of risk one chooses as the basis for risk management. Much detail about conservatism follows in this appendix of the report, but the essence of the disagreement between supporters of this proposal and supporters of the alternative position is simple; the former group believes that it is both prudent and scientifically justified to make reasonable attempts to favor errors of overestimation over those of underestimation. More importantly, it believes that not to do so would be both imprudent and scientifically questionable. This is no mere tautology, but encapsulates the disagreement with others who would argue that to eschew prudence is to advocate something "value-neutral" (and hence a morally superior position for scientists to espouse) and something more "scientific."

The controversies over conservatism are heightened by ambiguous definitions and uses of the term. The following section explains three dichotomies about the precise possible meanings of conservatism, in order to clarify some of the objections to it, and to foreshadow some of the features of this proposal for a principle of "plausible conservatism":

(1) *The distinction between prudence and misestimation*. When a particular estimate of risk is criticized as being "too conservative," that criticism can

mean one or both of two different things. The critic may actually mean that the assessor has chosen an estimate of risk which is designed to reduce the probability of errors of underestimation, but one which the critic deems overly zealous in that regard. In other words, one person's "prudence" may be another person's "overkill," although that distinction alone is purely one of differing personal values. On the other hand, the critic may instead mean that flaws in the estimation of a risk cause the estimate to be more skewed in the direction of prudence than the assessor himself intends, or than the risk manager comprehends. Such a criticism may not involve any personal value judgments. For example, the assessor may believe that a particular estimate falls at around the 95th percentile of the uncertainty distribution of the unknown risk; such an estimate would have a 5% probability of being an underestimate of the risk. If, in fact, the estimate given is so tilted towards minimizing underestimation that it falls at (say) the 99.9th percentile of the distribution, then the process would have built in more prudence than either party intended. It is possible that in many of the instances where EPA is under fire for allegedly being "too conservative," critics are espousing differing value judgments in addition to (or instead of) trying to point out disparities between the intended and actual level of conservatism. There is, as discussed below, little empirical evidence to suggest that EPA's potency, exposure, or risk estimates are markedly higher than estimates embodying a reasonable degree of prudence (i.e., the conventional benchmarks of the 95th or 99th percentiles that statisticians use). However, supporters of the proposal detailed in this appendix are clearly opposed to systematic misestimation, if and when it exists. We stress that our version of "plausible conservatism" in risk assessment does not allow EPA to adopt unreasonable assumptions or rely upon biased parameter values, and we believe that the entire committee's consensus recommendations in Chapters 9 and 10 will help combat this tendency, if it exists, and help shed light, rather than heat, on the question of whether EPA's risk estimates are more conservative than they are intended to be.

(2) *The distinction between conservatism as a response to uncertainty or as a response to variability*. This important distinction bears upon the legitimacy of criticisms of conservatism. The two issues of uncertainty and variability involve different motivations and produce different results, even though the same terms and mathematical procedures are used to deal with each and though they may at times be hard to separate operationally. This appendix of the report deals primarily with the former, and then generally with the subcategory of conservatism regarding model uncertainty. In this discussion of uncertainty issues, because we are dealing with lack of knowledge as to the true value of risk, the science-policy balancing of errors of underestimation and overestimation does suggest the common aphorism of "better safe than sorry." The science-policy response to variability, on the other hand, involves coping with differences among people in their exposures or susceptibilities to adverse effects—that is,

deciding with certainty (or with no additional uncertainty beyond that due to not knowing which models apply) who or what should be protected. In such cases, deciding how conservative to be in light of this variability is *not* about "being better safe than sorry," but involves a decision about who merits being safe and who may end up being sorry. Here, as elsewhere in the CAPRA report, the committee refrains from coming to policy judgments about how EPA should draw such lines in general or in particular. In this discussion, we simply stress that EPA should not let criticisms of its responses to uncertainty confuse it or necessarily cause it to rethink its responses to variability.[2]

(3) *The distinction between the "level of conservatism" and the "amount of conservatism"*. Any estimate of an uncertain risk embodies conservatism, if any at all, in both relative and absolute senses. Here the new terms "level of conservatism" and "amount of conservatism" are coined to codify the difference, respectively, between the relative and absolute meanings of the term. The "level of conservatism" is a relative indicator of how unlikely the assessor deems it that the estimate will fall below the true value of risk; thus, a 99th percentile estimate embodies a higher "level of conservatism" (four percentile points higher) than does a 95th percentile estimate. The "amount of conservatism," in contrast, is an absolute measure of the mathematical difference between the estimate itself and the central tendency of the unknown quantity. Thus, it is quite possible to have a high "level" and a small "amount" simultaneously, or vice versa. For example, scientists might know the speed of light to a high degree of precision, and report a 99th percentile upper confidence limit of 186,301 miles/sec. and a "best estimate" of 186,300 miles/sec. (here the absolute amount of conservatism would be 1 mile/sec.). On the other hand, when uncertainty is large, even a modest "level" (say the 75th percentile) may introduce a large amount of conservatism in absolute terms. These two concepts are related in a straightforward manner with important policy implications. As scientific knowledge increases and uncertainty decreases, the absolute difference between the central tendency and any particular upper percentile will also decrease. Therefore, agencies could try and maintain a fixed level of conservatism over time and yet expect that the absolute amount of conservatism, and thus the practical impact of attempts to shift the balance in favor of overestimation, will become progressively less and less important. When uncertainty is reduced to minimal levels, the conservative estimate and the central tendencies will become so similar that the distinction becomes

[2] For two reasons, we believe it is logically consistent to espouse a principle of "plausible conservatism" with regard to model uncertainty and not explicitly recommend the same response to variability: (1) as a pragmatic matter, we believe scientists have more that they alone can contribute to a discussion of how to choose among competing scientific theories than they have to contribute to a discussion of what kind of individuals EPA should try to protect; and (2) we believe the public has more clearly expressed a preference for "erring on the side of safety" when the truth is unknown than it has regarding how much protection to extend to the extremes of variability distributions.

practically irrelevant, although risk managers and public can remain assured that the *probability* of errors of underestimation remains constant and relatively small.

Inherent Advantages of "Plausible Conservatism"

It is perplexing to some members of this committee (and to many in the general populace) that the presumption that society should approach uncertain risks with a desire to be "better safe than sorry" has engendered so much skepticism. After all, perhaps it should instead be incumbent upon opponents of conservative defaults to defend their position that EPA ought to ignore or dilute plausible scientific theories that, if true, would mean that risks need to be addressed concertedly. That view, whatever its intellectual merits, seems at the outset not to give the public what it has consistently called for (explicitly in legislation and implicitly in the general conduct of professions ranging from structural engineering to medicine to diplomacy): namely, the attempt to guard against major errors that threaten health and safety. But the proposal for risk assessment based on "plausible conservatism" came about largely because of the wide variety of *other* factors supporting it, whether viewed through the lenses of logic, mathematics, procedure, or political economy. The following brief accounting of some of the virtues of a conservative orientation may seem somewhat superfluous, especially given the statements of earlier NRC committees on the topic.[3] However, this committee's decision not to endorse "plausible conservatism" by consensus has prompted this more thorough enumeration of some factors some members had though were uncontroversial:

A. *"Plausible Conservatism" Reflects the Public's Preference Between Errors Resulting in Unnecessary Health Risks and those Resulting in Unnecessary Economic Expenditures*.

An examination of the two kinds of errors uncertainty in risk can cause supports the conclusion that society has not been indifferent between them. One type of error (caused by the overestimation of risk) leads to more resources invested than society would optimally invest if it knew the magnitude of the risk precisely. The other type (caused by underestimation of risk) leads to more lives lost (or more people subjected to unacceptably high individual risks) than society would tolerate if there was no uncertainty in risk. Whether the aversion to the latter type of error is due to the greater irreversibility of its consequences

[3] For example, consider this recent statement of the BEST Committee on Environmental Epidemiology (NRC, 1991): "public health policy requires that decisions be made despite incomplete evidence, with the aim of protecting public health in the future."

compared to the former,[4] the importance of regret (Bell, 1982) in most individual and social decision-making,[5] or other factors is beyond our capacity to answer. What matters is, do Congress and the public view risk management as a social endeavor that should strive both for scientific truth and for the prudent avoidance of unnecessary public health risks, and therefore do not view risk assessment as purely an exercise in coming as close to the "right answer" as possible? If this is so, then the competing proposal offered in Appendix N-2 espouses an unscientific value judgment, and one that also is unresponsive to social realities.

A counter-example may be illustrative here. In its recent indictment of conservatism in Superfund risk assessment, an industry coalition drew an extended analogy to link EPA's risk estimates with inflated predictions of the amount of time it would take someone to take a taxi ride to Dulles Airport (Hazardous Waste Cleanup Project, 1993). But this particular personal decision seems to be another prime example of where individuals and society would clearly prefer conservative estimates. As demonstrated below, *any* level of conservatism (positive, zero, or negative) corresponds to some underlying attitude towards errors of overestimation and underestimation. In this case, a conservative estimate of travel time simply means that the traveller regards each minute she arrives at the airport after the plane leaves as more costly to her than each minute of extra waiting time caused by arriving before the plane leaves. It is hardly surprising to conclude that a rational person would not be indifferent, but would rather be 10 minutes early than 10 minutes late to catch a plane. If, hypothetically, someone advising the traveller told her he wasn't sure whether the airline she chose would have a single ticket agent (and a 20-minute long line) or a dozen agents (and no line), it seems hard to believe that she would ask for a "best estimate" between zero and 20 minutes and allow only that much time (and even less likely she would assume that the long line simply couldn't happen). As long as the more "conservative" scenario was plausible, it would tend to dominate her thinking, simply because the decision problem is not about arriving at exactly the right moment, but about balancing the costs of a very early arrival against the *qualitatively* different costs of even a slightly late arrival. Again, reasonable people may differ widely about how large either asymmetry should be, but supporters of "plausible conservatism" are hard pressed to imagine not

[4] It is possible that profligacy in economic resources invested may also lead to adverse health consequences (MacRae, 1992). However, this "richer is safer" theory is based on controversial data (Graham et al., 1993), and at most offsets in an indirect way the more direct and irreversible consequences of underregulation in the eyes of the public

[5] Anticipation of regret tends to make people choose courses of action that are less likely to leave them with the knowledge that they failed to take another available action that would have been much less damaging.

admitting that some adjustment to make catching the plane more likely, or reducing the risk more probable, aligns with the expressed desires of the public.

B. *Conservative Defaults Help Increase the Chances that Risk Estimates Will Not be "Anti-Conservative."*

There are two different mathematical aspects of risk assessment under uncertainty that mitigate in favor of a conservative approach to selection of default options. Both factors tend to make risk estimates generated from conservative models less conservative than they might appear at first glance, and thus tip the balance further in favor of such models as minimally necessary to support prudent decisions.

Let us assume at the outset that the assessor and decision-maker both desire that at the very least, risk estimates should not be "anti-conservative," that is, not underestimate the mean (arithmetic average) of the true but unknown risk. The mean, after all, is the minimum estimator that a so called "risk-neutral" decision-maker (e.g., a person who is not actually trying to catch a plane, but who stands to win a wager if she arrives at the airport either just before *or* just after the plane leaves) would need in order to balance errors of overestimation and underestimation. In this regard, there exists a basic mathematical property of uncertain quantities that introduces an asymmetry. For non-negative quantities (such as exposures, potencies, or risks), the uncertainties are generally distributed in such a way that larger uncertainty increases the arithmetic mean, due to the disproportionate influence of the right-hand tail. For example, if the median (50^{th} percentile) of such an uncertainty distribution was X, but the assessor believed that the standard error of that estimate was a factor of 10 in either direction, then the 90^{th} percentile (19X) and the arithmetic mean (14X) would be nearly identical; if the uncertainty was a factor of 25 in either direction, the mean and the 95^{th} percentile would be virtually identical (see Table 9-4). Some of the most familiar examples of the need to impose a moderate "level of conservatism" in order not to underestimate the mean come from empirical data that exhibit variability. For example, it is unlikely, even in a state that includes areas of high radon concentration, that a randomly selected home would have a radon concentration exceeding approximately 10 picocuries/liter. Yet the mean concentration for all homes in that state might equal or even exceed 10 because of the influence on the mean of the small number of homes with much higher levels.[6]

[6] This mathematical truism that the more uncertainty, the greater the level of conservatism required not to underestimate the mean, seriously undermines one of the major claims made by those who accuse EPA of "cascading conservatism." If each of a series of uncertain quantities is distributed in such a way that a reasonably conservative estimator (say, the 95^{th} percentile) approximates or even falls below the mean of that quantity, then the more steps in the cascade the *less* conservative the output becomes with respect to the correct risk-neutral estimator.

The other basic mathematical advantage of introducing some conservatism into the scientific inferences that are made is the expectation that there may be other factors unknown to the assessor which would tend to increase uncertainty. This becomes a stronger argument for conservatism if one believes that more of these unknown influences would tend to increase than to decrease the true risk. Although it seems logical that factors science has not yet accounted for (such as unsuspected exposure pathways, additional mechanisms of toxicity, synergies among exposures, or variations in human susceptibility to carcinogenesis) would tend to add to the number or severity of pathways leading to exposure and/or greater risk, it is possible that "surprises" could also reveal humans to be more resistant to pollutants or less exposed than traditional analyses predict.

C. *"Plausible Conservatism" Fulfills the Statutory Mandate under which EPA Operates in the Air Toxics (and many other) Programs.*

The policy of preventive action in the face of scientific uncertainty has long been part of the Clean Air Act, as well as most of the other enabling legislation of EPA. Two key directives run through many of the sections of the Clean Air Act in this regard. First, various sections of the Act direct EPA to consider not merely substances that have been shown to cause harm, but those that "may reasonably be anticipated" to cause harm. As the D.C. Circuit court stated in its 1976 decision in *Ethyl Corp. v. EPA*, "commonly, reasonable medical concerns and theory long precede certainty. Yet the statutes and common sense demand regulatory action to prevent harm, even if the regulator is less than certain that harm is otherwise inevitable." Similarly, the Act has long required standards for air pollutants to provide "an ample margin of safety to protect public health." The leading case on the interpretation of Section 112, the 1987 case of *Natural Resources Defense Council v. EPA*, declared that

> In determining what is an "ample margin" the Administrator may, and perhaps must, take into account the inherent limitations of risk assessment and the limited scientific knowledge of the effects of exposure to carcinogens at various levels, and may therefore decide to set the level below that previously determined to be "safe."…[B]y its nature the finding of risk is uncertain and the Administrator must use his discretion to meet the statutory mandate.

Again, support for the idea that "plausible conservatism" is the most rational approach for EPA to take is not necessarily based on a reading of the various statutes. After all, it is possible that the statutes may be changed in the near or far future. However, it seems central to EPA's mission that the Agency consider whether it is necessary to prevent or minimize adverse events, even events of low probability. Therefore, the Agency inevitably will find it necessary to use risk assessment techniques that are sensitive enough to reflect the risks of those events. At a minimum, its techniques must explore the nature of possible extreme outcomes, as a prelude to science-policy choices as to whether to factor those extremes into its risk characterizations. *In essence, conservatism in the*

choice of default options is a way of making risk assessment a sensitive enough device to allow risk managers to decide to what extent they can fulfill the intent of the enabling legislation. For this reason, members of the committee advanced the proposition, which proved eventually to be controversial within the committee, that "plausible conservatism" gives decisionmakers some of the information they need to make precautionary risk management decisions.

D. *It Respects the Voice of Science, Not Only the Rights of Individual Scientists*.

By declaring that defaults would be chosen to be both scientifically supportable and health-protective, and that scientists would have to examine alternative models by these two criteria, EPA could help ensure that science will assume the leading role in defining evolving risk assessment methodology. Some have asserted that it shows disrespect for science to posit any standard for departure from defaults other than one that simply requires EPA to adopt "new and better science at the earliest possible time." But surely there is a generally inverse relationship between the amount of knowledgeable controversy over a new theory and the likely "staying power" and reliability of such "new science." At the extremes, EPA could either change its defaults over and over again with each new individual voice it hears complaining that a default is passé, or never change a default until absolute scientific unanimity had congealed and remained unshakable for some number of years. The "persuasive evidence" standard proposed here (see below) clearly falls between these two extremes. It reflects our belief that standards which rely more on scientific consensus than on the rights of individual scientists dissatisfied with the current situation are in fact more respectful of science as an institution.

The only cost to a standard that values scientific consensus over "heed the loudest voice you hear" is that advocates of "new science" need to persuade the mainstream of their colleagues that new is indeed better. This standard is in fact a bargain for scientists, because it buys credibility in the public arena and some degree of immunity against being undercut by the *next* new theory that comes along. And, in addition to this give-and-take principle that elevates respect for scientific decisions by valuing the concord of scientists, advocates of "new science" must appreciate that the twin standards of plausibility and conservatism in fact *remove* a major source of arbitrariness in EPA's science-policy apparatus. If the Agency merely held up its defaults as unconnected "rules we live by" and required scientists to prove them "wrong," then the charge of bureaucracy-over-science would have merit. But this recommendation for EPA to reaffirm or rethink the set of defaults as "the most conservative of the plausible spectrum" sends a clear signal to the scientific community that each default only has merit insofar as it embodies those twin concepts, and gives scientists two clear bases for challenging and improving the set of inference assumptions.

E. *It Generates Routinely those Risk Estimates Essential to Various EPA Functions*.

The committee was also unable to reach agreement on the details of what roles "nonconservative" estimates should play in standard setting, priority setting, and risk communication, although the committee's recommendations in Chapter 9 reflect its belief that such estimates have utility in all of these arenas. However, no one has suggested that "nonconservative" estimates should drive out estimates produced via "plausible conservatism," but rather that they should supplement them. Indeed, the committee agrees that conservative estimates must be calculated for at least two important risk assessment purposes: (1) the foundation of the iterative system of risk assessment the committee has proposed is the screening-level analysis. Such analyses are solely intended to obviate the need for detailed assessment of risks that can to a high degree of confidence be deemed acceptable or *de minimis*. By definition, therefore, screening analyses must be conservative enough to eliminate the possibility that an exposure that indeed might pose some danger to health or welfare will fail to receive full scrutiny; and (2) even if EPA decided to use central-tendency risk estimates for standard-setting or other purposes, it would first have to explore the conservative end of the spectrum in order to have any clear idea where the expected value of the uncertain risk (as discussed above, the correct central-tendency estimate for a risk-neutral decision) actually falls. Because of the sensitivity of the expected value of a distribution to its right-hand tail, one cannot simply arrive at this midpoint in one step.[7]

For both reasons, risk assessment cannot proceed without the attempt to generate a conservative estimate, even if that estimate is only an input to a subsequent process. Therefore, the only argument among us is whether to modify or discard such estimates for some purposes other than screening or calculation of central tendencies, not whether they should be generated at all. Either way, a set of default assumptions embodying "plausible conservatism" must play some role.

F. *It Promotes an Orderly, Timely Process that Realistically Structures the Correct Incentives for Research*.

Many observers of risk assessment have pointed out that the scientific goal of "getting the right answer" for each risk assessment question conflicts directly with the regulatory and public policy goals of timeliness and striking a balance

[7] See Table 9-4 for various calculations showing how if the uncertainty is distributed continuously, the arithmetic mean can be very sensitive to the conservative percentiles. If instead, the uncertainty is dichotomous (say, the risk was either Y or zero depending on which of two models was correct), the expected value would depend *completely* on the value of Y and the subjective probability assigned to it. *In either case, the upper bound must be estimated before the mean can be*.

between limited resources available for research and those available for environmental protection itself. The committee agreed that too much emphasis on fine-tuning the science can lead to untoward delay; our real disagreement again comes down to the question of how to initiate and structure the process of modifying science-based inferences. As discussed in the preceding paragraph, one advantage of starting from a conservative stance and declaring the true central tendency as the ultimate goal is that it arguably is easier to move towards this desired midpoint (given the influence of the conservative possibility on it) than to start by trying to guess where that midpoint might be. There is also a procedural advantage to a conservative starting point, however, which stems from a frank assessment of the resources and natural motivations available to different scientific institutions. Some of us believe that an evaluation of the relative effort over the last decade or so devoted to positing and studying less conservative risk models (e.g., threshold and sublinear extrapolation models, cases where humans are less sensitive than test animals) *versus* the converse (e.g., synergies among exposures, cases where negative rodent tests might not spell safety for humans) reveals an asymmetry in research orientation, with the former type of research garnering much more resources and attention than the latter. This orientation is not necessarily either pernicious or unscientific, but EPA should make use of it rather than pretend it does not exist. The best way for the Agency to do so, we believe, is to begin with a stance of "plausible conservatism" and establish explicit procedures, based on peer review and full participation, that demonstrate convincingly that the Agency understands it must be receptive to new scientific information. This takes advantage of the tendency to preferentially test less conservative theories. Moreover, EPA must communicate to the public that a general tendency for risk estimates to become less conservative (in absolute terms) over time is not evidence of EPA bias, but of an open and mutual covenant between the Agency and the scientific community searching for better models.

G. *It Reflects EPA's Fundamental Public Mission as a Scientific/Regulatory Agency*.

As discussed below, advocates of "best estimates" frequently fail to consider how difficult, error-prone, and value-laden the search for such desirable end points can be. Since CAPRA has been asked to suggest improvements in the methodology by which EPA assesses risks from exposures to hazardous air pollutants, it is also incumbent upon us at least to remark on the purpose of such risk estimates. Part of our disagreement on the entire set of defaults issues arises because there are two purposes for risk estimates: to accurately describe the true risks, if possible, and to identify situations where risks might be worth reducing. Other government agencies also have to serve the two masters of truth and decision, yet their use of analysis does not seem to arouse so much controversy. Military intelligence is an empirical craft that resembles risk assessment in its reliance on data and judgment, but there have been few exhortations that the

Department of Defense (DOD) should develop and rely on "best estimates" of the probability of aggression, rather than on accepted estimates of how high those probabilities might reasonably be. There is room for vigorous descriptive disagreement about the extent of conservatism in DOD predictions, and for normative argument about the propriety thereof, but these are questions of degree that do not imply DOD should abandon or downplay its public mission in favor of its "scientific" mission.[8]

Specific Recommendations To Implement This Principle

Members of the committee who advocate that EPA should choose and modify its defaults with reference to the principle of "plausible conservatism" have in mind a very specific process to implement this principle, in order to accentuate its usefulness along the criteria discussed in the introduction to Part II of the report, and to minimize its potential drawbacks. In light of the controversy these four recommended procedures engendered within the committee, this section will emphasize what our vision of "plausible conservatism" does not involve or sanction, even though these features apparently were not sufficient to stanch the opposition to the proposal.

Step 1 In each instance within the emissions and exposure assessment or the toxicity assessment phase of risk assessment where two or more fundamentally different scientific (i.e., biological, physical, statistical, or mathematical) assumptions or models have been advanced to bridge a basic gap in our knowledge, EPA should first determine which of these models are deemed "plausible" by knowledgeable scientists. As an example, let us assume that scientists who believe benign rodent tumors can be surrogates for malignant tumors would admit that the opposite conclusion is also plausible, and *vice versa*. Then, from this "plausible set," *EPA should adopt (or should reaffirm) as a generic default that model or assumption which tends to yield risk estimates more conservative than the other plausible choices*. For example, EPA's existing statement (III.A.2 from the 1986 cancer guidelines) that chemicals may be radiomimetic at low doses, and thus that the linearized multistage model (LMS) is the appropriate default for exposure-response extrapolation, is not a statement of scientific fact, but is the preferred science-policy choice, for three reasons: (1) the scientific conclusion that the LMS model has substantial support in biologic theory and

[8] Note that these 7 advantages of conservatism are not an exhaustive list. Others that could have been discussed include: this proposal is close to what EPA already does; it jibes with the rest of the CAPRA report; it is also motivated by some pure management issues, notably the potential problem of a bias towards exaggeration in the cost figures that risk estimates are compared to.

observational data (so it cannot be rejected as "absolutely implausible"); (2) the scientific conclusion that no other extant model has so much *more* grounding in theory and observation so as to make the LMS fail a test of "relative plausibility"; and (3) the empirical observation that the LMS model gives more conservative results than other plausible models.[9]

Step 2 Armed with this set of scientifically supportable and health-protective models, EPA should then strive to amass and communicate information about the uncertainty and variability in the parameters that drive these models.[10] *The uncertainty distributions that result from such analyses will permit the risk manager to openly choose a level of conservatism concordant with the particular statutory, regulatory, and economic framework, confident that regardless of the level of conservatism chosen, the risk estimate will reflect an underlying scientific structure that is both plausible and designed to avoid the gross underestimation of risk*. In Chapters 9 and 11, the committee supports this notion that the level of conservatism should be chosen quantitatively with reference to parameter uncertainty and variability, but qualitatively with reference to model uncertainty (i.e., under this proposal, models would be chosen to represent the "conservative end of the spectrum of plausible models"). Although the "plausible conservatism" proposal *per se* was not unanimously agreed to, the entire committee does share the concern that attempts to precisely fine-tune the level of conservatism implicit in the model structure may lead to implausible or illogical compromises that advance neither the values of prudence nor of scientific integrity.

Step 3 EPA should then undertake two related activities to ensure that its resulting risk estimates are not needlessly conservative, or misunderstood by

[9] EPA should be mindful of the distinction between "plausible as a general rule" and "plausible as an occasional exception" in choosing its generic defaults, and only consider the former at this stage (i.e., if a particular model is not plausible as a means of explaining the general case, it should be reserved for consideration in specific situations where a departure may be appropriate). For example, a more conservative model than the LMS model, a "superlinear" polynomial allowing for fractional powers of exposure (Bailar et al., 1988), may be plausible for certain individual chemicals but appears at present not to pass a consensus threshold of scientific plausibility as a generic rule to explain all exposure-response relationships. On the other hand, less conservative models such as the M-V-K model do cross this threshold as plausible-in-general but would not yet qualify as appropriate generic defaults under the "plausible conservatism" principle.

[10] As the committee discusses in its recommendations regarding "iteration," the level of effort devoted to supplanting point estimates of parameters with their corresponding uncertainty or variability distributions should be a function of the "tier" dictated by the type and importance of the risk management decision. For screening analyses, conservative point estimates within the rubric of the prevailing models will serve the needs of the decision, whereas for higher-tier analyses uncertainty distributions will be needed.

some or all of its audience. These steps are important even though by definition, risk estimates emerging from a framework of "plausible conservatism" cannot be ruled out as flatly impossible without some empirical basis (since they are based on a series of assumptions, each of which has some scientific support, the chain of assumptions must also be logically plausible, if perhaps unlikely). As some observers have pointed out, however, such estimates may be higher than some judge as necessary to support precautionary decisions (Nichols and Zeckhauser, 1988; OMB, 1990). A quantitative treatment of uncertainty and an explicit choice of the level of conservatism with respect to parameter uncertainty, as recommended here and in Chapter 9, will help minimize this potential problem. EPA can mitigate these concerns still further by: (1) calibrating its risk estimates against available "reality checks," such as the upper confidence limit on human carcinogenic potency one can sometimes derive in the absence of positive epidemiologic data (Tollefson et al., 1990; Goodman and Wilson, 1991) or physical or observational constraints on the emissions estimates used or the ambient concentration estimates generated by the exposure models used; and (2) clearly communicating that its risk estimates are intended to be conservative (and are based on plausible but precautionary assumptions). In improving its risk communication, EPA should try to avoid either underestimating the level of conservatism (e.g., EPA's current tendency to imply that its estimates are "95th percentile upper bounds" when they really comprise several such inputs that, in combination with other nonconservative inputs, might still yield an output more conservative than the 95th percentile) or overstating the amount of conservatism (e.g., EPA's tendency to state that all its potency estimates "could be as low as zero" even in cases when there is little or no support for a threshold model or when the estimates are based on human data). In essence, the thrust of this step of our proposal is to further distinguish between the concepts of prudence and misestimation discussed above, and to discourage the latter practice so that critics of conservatism will have to come to grips with (or abandon) their opposition to the former.

Step 4 Finally, (a point to which the entire committee agreed) EPA should clarify its standard for how it decides it should replace an existing default assumption with an alternative (either as a general rule or for a specific substance or class of substances). Currently, EPA only uses language implying that each default shall remain in force "in the absence of evidence to the contrary," without any guidance as to what quality or quantity of evidence is sufficient to spur a departure or how to gauge these attributes (or, of course, any guidance if any principle other than one of evidentiary quality should govern the choice among alternatives). Here, a specific test for structuring departures from defaults is proposed. Specifically, EPA should go on record as supporting departures from defaults whenever "*there exists persuasive evidence, as reflected in a general consensus of knowledgeable scientists, that the alternative assumption (model)*

represents the conservative end of the spectrum of plausible assumptions (models)." This language was carefully chosen, based on substantial debate within the committee, to achieve several objectives:

- to strike a balance between having defaults that are too rigid and ones that change too often (and that tend to change for unpredictable and perhaps even self-contradictory reasons). The requirement for "persuasive evidence," and the deference to scientific consensus as an indicator of this quality of evidence, yields an explicit standard that is neither as difficult to meet as "beyond a reasonable doubt" would be (a single scientific dissenter could thwart the process if EPA used this standard) nor as flexible and subject to backtracking as language such as "preponderance of the evidence" or "best available scientific opinion" would be. No other standard we considered seems to strike a better balance between elusive scientific unanimity and evanescent (and perhaps illusory) scientific plurality.
- to reaffirm the principle of "plausible conservatism" in the inferences made as time passes and scientific knowledge improves. If defaults changed solely on the basis of "correctness," there would be no continuity among the assumptions EPA uses in the way each attempts to cope with uncertainty (only the overconfident affirmation that each default is "correct" in spite of the uncertainty). Instead, this standard makes all assumptions/models comparable, whether they are holdovers from the 1986 guidelines or newly-adopted alternatives; they will all represent the choices deemed to be both supportable and health-protective. In other words, under this system the *level of conservatism* will remain constant (at least on a qualitative scale) while the *amount of conservatism* will generally decrease over time in lockstep with the progress of scientific knowledge.[11] Thus, control of pollutant sources can generally become less stringent over time without lessening the level of assurance that public health goals are being met.
- to encourage, under the iterative approach called for elsewhere in this report, the use of more data and more sophisticated models without cumbersome processes for approving their use. The "plausible conservatism" standard recommended here acknowledges that simplicity in risk assessment is useful for certain risk management purposes but is not an end in itself. Thus, the actual default model for certain atmospheric transport calculations might well be a more complex version of a simpler and more conservative screening model (e.g.,

[11] In special circumstances, a new scientific consensus may emerge that a model or assumption that is *more* conservative than the default is clearly plausible, either as a general rule or for specific chemicals or exposure scenarios. In such cases, the absolute amount of conservatism will increase. Although this asymmetry results in a *de facto* lower procedural threshold for adopting more conservative models than less conservative ones, the requirement implicit in the standard for a consensus about plausibility should limit the frequency with which the former type of departures will occur.

Lagrangian versus box models). Assessors would be free to use the simpler model for screening purposes without threatening the primacy of the more complex model for higher-tier risk assessments. An excellent example of this accommodation of multiple assumptions that each embody "plausible conservatism" might be the use of PBPK models in higher-tier assessments versus a generic scaling factor (such as body weight to the 0.67 or 0.75 power) in lower-tier assessments. Perhaps EPA should consider designating a particular PBPK model as the default option for interspecies scaling, while reiterating that the scaling factor (which is itself a simple pharmacokinetic model) would also be an appropriate default for less resource-intensive applications.[12]

- to encourage greater use of peer review and other mechanisms to increase the scientific community's role in the evolving selection of preferred models. Implicit in this standard is the intent that EPA should continue to use its Science Advisory Board and other expert bodies to determine when general scientific consensus exists. Workshops, public meetings, and other devices should increasingly be used to guarantee, as much as possible, that EPA's risk assessment decisions will be made with access to the best science available and the full participation of the entire expert community.

Pitfalls Of Our Proposal; Comparison With Alternatives

Some of the criticisms raised against conservatism in risk assessment have substantial merit, and are applicable to this proposal to include conservatism in the choice of default options. EPA can minimize some of these pitfalls by following other recommendations made in this appendix and elsewhere in the report. For example, the problem that conservatism can lead to incorrect risk comparisons and priority-setting decisions can be remedied in part by striving to make the "level of conservatism" explicit and roughly constant across assessments, and by generating additional estimates of central tendency (perhaps even derived via subjective weights applied to different basic biological theories) for use in ranking exercises only.[13]

Similarly, there is a legitimate concern that the policy of conservatism can stifle research if EPA is perceived as uninterested in

[12] The only important caveat to this principle, which would apply to the transport model example as well as the PBPK example, is that with the addition of new model parameters (e.g., partition coefficients and rate constants in the PBPK case), the uncertainty and interindividual variability in those parameters must be estimated and incorporated into an explicit choice of a level of conservatism (see recommendation in Chapter 9).

[13] We note that risk ranking under uncertainty is a complicated and error-prone process, regardless of whether conservative, average, or other point estimates are used to summarize each risk. The medians or means of two risk distributions can be in one rank order while the upper bounds could well be in the opposite order; no single ranking alone is correct.

any new information that might show the risk has been overstated; the emphasis here on scientific consensus does tend to slow the adoption of less conservative models at their early stages of development, but this should neither discourage thorough research nor discourage researchers from submitting quality data which EPA could readily incorporate into its existing model structure regardless of what effect it would have on the risk estimate.

The fundamental concern about conservatism is that it has led to systematic exaggeration of all environmental health problems and has encouraged wasting of scarce resources on trivial risks. The latter part of this charge is a subjective matter of economic and social policy that falls outside this committee's purview. And while the former concern is an empirical one, it has sparked a vigorous debate that is far from resolved. On one side, those convinced that EPA's procedures yield estimates far above the true values of risk can cite numerous examples where individual assumptions seem to each contribute more and more conservatism (Nichols and Zeckhauser, 1988; OMB, 1990; Hazardous Waste Cleanup Project, 1993). Others believe the evidence shows that current procedures embody a mix of conservative, neutral, and anti-conservative assumptions, and that the limited observational "reality checks" available suggest that existing exposure, potency, and risk estimates are in fact not markedly conservative (Allen et al., 1988; Bailar et al., 1988; Goodman and Wilson, 1991; Finley and Paustenbach, in press; Cullen, in press).

The practical and constructive question EPA must grapple with, however, is not whether "plausible conservatism" is ideal, but whether it is preferable to the alternative(s). The primary alternative to this proposal (Appendix N-2) directs EPA risk assessors to use defaults on the basis of the "best available scientific information," with the apparent goal of generating central-tendency estimates (CTEs) of risk. According to proponents of this approach, there is a clear boundary line between the "objective" activity of risk assessment and the value-laden activity of risk management, and the imposition of conservatism (if any) should occur in the latter phase, with managers adding "margins of safety" to make precautionary decisions out of the CTEs. In comparing this proposal with the alternative, it is important to consider the two foundations of the latter approach, the CTE (or "most scientific estimate") and the margin of safety, and ask whether either concept is really as appealing as it may sound.

The margin of safety idea is problematic, for one obvious reason: *it is only through exploring the conservative models and parameter values that analysts or managers can have any idea what they are trying to be "safe" from*. Perhaps it would be ideal for the manager rather than the assessor always to tailor the level of conservatism, but in reality, only the assessor can initially determine for the manager what a "conservative decision" would entail, because the assessor has the access to information on the spectrum of plausible values of risk. Applying any kind of generic safety factor to CTEs of risk would certainly result in a haphazard series of decisions, some (much) more conservative than a reasonable

degree of prudence would call for, others (much) less so. Besides, taken as a whole the committee's report returns some discretion and responsibility to the risk manager that assessors have admittedly usurped in the past by presenting point estimates alone. The committee's emphasis on quantitative uncertainty and variability analysis gives risk managers the ability to tailor decisions so that the degree of protection (and the confidence with which it can be ensured) are only as stringent as they desire. But in the narrow area of model uncertainty, this proposal deems it unwise to encourage risk managers to *guess at* what a protective decision would be, by censoring information about models which, although conservative, are still deemed by experts to be plausibly true.

The CTE also has potentially fatal problems associated with it. Even if the models used to construct CTEs are based on "good science," we have argued (above) that these estimates are not designed to predict the expected value of potency, exposure, or risk (for which the conservative end of the spectrum must be explored and folded in), but instead are surrogates for other central-tendency estimators such as the median or mode (maximum likelihood). These latter estimators generally do not even give neutral weight to errors of underestimation and overestimation, and hence must be regarded as "anti-conservative." But advocates of CTEs have also failed to consider the problems of the models from whence they come. The following are four examples, illustrating four archetypes of central-tendency estimation, which suggest that on a case-by-case basis, "good science" may not be all its proponents advertise it to be:

Case 1: *"More science" merely means more data*. Some of the alternative CTE estimates advocated by critics of conservatism are alleged to be more scientific because they make use of "all the data at hand." This distinction is hardly a cut-and-dried one, however. For example, consider the current EPA default of using the bioassay result from the most sensitive of the (usually no more than four) sex-species combination of rodent tested. Call this potency estimate "A," and the alternative that could be derived by pooling all (four) data sets as "ABCD." Assuming that we know very little about the relative susceptibilities of different varieties of rodents *versus* the average human (in general or for the particular substance at issue), we must logically admit that it is possible the true risk to the average human may be greater than that implied by A, less than that implied by ABCD, or somewhere in between. One could prefer ABCD to A on the basis of a different value judgment about the costs of overestimation and underestimation, but the only "scientific" difference is that ABCD makes use of more data. But "purchasing" an array of data is akin to buying cards in a blackjack game: "more is better" only holds true as long as all the individual elements are valuable rather than otherwise. Assuming rodent varieties A through D differ significantly (or we wouldn't be quarreling over the two estimators), then humans must either be most like variety A or most like one of the other three. If the former, then data points B, C, and D *dilute* and ruin what is already in fact

the "best estimate"; if the latter, then more is indeed better (in the sense of moving us closer to the truth). Therefore, EPA's true dilemma is whether the additional data are more likely to hurt or to help, and *this too is a policy judgment about balancing estimation errors*, not a simple matter of "good science." However, as a matter of process and of implementation, there is a clear difference between a policy of choosing A and a policy of choosing ABCD. The former policy sets up incentives to actually advance the scientific foundation and get to the truth of which sex/species is the best predictor in specific or in general; when such information becomes available, "good science" will justifiably carry the day. On the other hand, the latter policy only encourages additional rote application of current bioassay designs to generate more data that assessors can pool.

A related example in the exposure assessment arena is discussed in Chapter 10. A CTE of approximately 7 years of exposure to a typical stationary source of toxic air pollutants is indeed based on much more data (in this case, data on the variation in the number of years a person stays at one residence before moving) than is the standard 70-year assumption EPA has used. But as noted in Chapter 10, those data, although valid at face value, may speak to a different question than the one EPA must address. To ensure that individual lifetime risk is correctly calculated in a nation containing thousands of such sources, EPA would need to consider data not only on years at one residence, but also on the likelihood (that we consider substantial) that when someone moved away from proximity to a source, he or she would move to an area where there is still exposure to the same or similar carcinogens. In both examples, "a great deal more data" (on interspecies susceptibility or on autocorrelation of exposure rates as people move, respectively) would certainly be preferable to EPA's *status quo* assumption, but questions arise as to whether "a little more data" help or hurt the realism of the calculations.

Case 2: *"More science" means constructing chimeras out of incompatible theories*. One brand of CTE that has gained some currency in recent years allegedly provides a means of incorporating all of the plausible scientific models, much as meta-analysis incorporates all of the available epidemiologic studies or bioassays on a particular compound. Unfortunately, there may be a world of difference between pooling related data sets and averaging incompatible theories. In Chapter 9, we discuss the obvious pitfalls of such hybrid CTEs, which arguably confuse rather than enrich the information base from which the risk manager can choose a course of action. For example, when faced with two conflicting theories about the potency of TCDD, EPA arguably should not have tried to change its potency estimate to "split the difference" between the two theories and make it appear that new science had motivated this change (Finkel, 1988). Rather, EPA could have achieved the same risk management objective by loosening regulatory standards on TCDD if it felt it could justify this on the grounds that there was a significant probability that the existing risk estimate

was excessively conservative. The committee could not agree on what sort of advice to give decisionmakers when some risk is either zero (or nearly zero) or is at some unacceptably high level X, depending on which of two fundamentally incompatible biologic theories is in fact the correct one. The committee did agree, however, that analysis should certainly not report only a point estimate of risk equal to (1-*p*)X, where *p* is the subjective probability assigned to the chance that the risk is (near) zero. In the specific context of default options, this proposal remains that EPA should retain its "plausible conservative" default until scientific consensus emerges that the alternative model supplants the default at the conservative end of the plausible set of model choices.

Case 3: *"More science" means introducing more data-intensive models without considering uncertainty or variability in the parameters that drive them.* This particular problem should be easy to rectify by incorporating the committee's recommendations in Chapters 9 and 10, but it is mentioned here because to date EPA has considered several departures from defaults (e.g., the case of methylene chloride, at least as interpreted by Portier and Kaplan, 1989) in which the level of conservatism may have changed abruptly because the parameters of the default model were assessed conservatively, but the parameters in the new model were either CTEs or point estimates of unknown conservatism. All of the burden should not fall upon purveyors of new models, however; EPA needs to level the playing field itself by systematically exploring the conservatism inherent in the parameters of its default models (for example, as we discuss in Chapter 11, is the surface area or 3/4 power correction a conservative estimate of interspecies scaling, or something else?).

Case 4: *"More science" is clearly an improvement but not airtight*. It is noteworthy that the most detailed case-specific reassessment of a default assumption, the CIGA case discussed in Chapter 6, has recently been called into question on the grounds that the new science casts serious doubt upon EPA's default as applied to existing animal data, but does not itself provide unimpeachable support for an alternative risk estimate (Melnick, 1993). We do not presume to reach any conclusion about this dispute, or about its implications for the general process of departing from defaults. As a matter of process, the CIGA case would probably meet the "persuasive evidence" test recommended here, and therefore one should not necessarily characterize EPA's acceptance of this new science as a mistake in policy. However, for purposes of risk communication, EPA should understand and emphasize that scientific consensus in issues such as these does not necessarily imply scientific truth.

Conclusions

In summary, EPA's choice between competing principles for choosing and departing from defaults has important and provocative implications for four areas of environmental science and EPA programs.

- *Values*. The choice between "plausible conservatism" and "best science" is inescapably one of science and of values. As this Appendix shows, both principles rely in part on science and decision theory, and both embody specific sets of value judgments. Unfortunately, some of the critics of "plausible conservatism" have shone a spotlight on the values inherent in that position while ignoring the value judgments inherent in the alternatives. We have argued that in many cases (and especially in the most practically important cases, where a dichotomy exists about whether a model predicting unacceptably high risk or a model predicting zero risk is correct), CTEs are difficult to derive and may not be meaningful. But even if CTEs were free of these pitfalls, one must recognize that choosing them over conservative estimates is a value-laden choice, and indeed that choosing *among* the three or more different brands of CTE, which may differ from each other by orders of magnitude in some cases, also requires value choices. The mode (maximum likelihood estimator) is a CTE with a particular purpose in decision theory; it maximizes the probability that the decision flowing from this estimate will be "right," without regard either to the direction or magnitude of deviations from this ideal. The median CTE seeks to balance the probability of the two types of error, again without regard to the magnitude of either; this, too, represents a particular value orientation. Finally, the mean attempts to balance the (unweighted) product of the probability and magnitude of errors of either type. The conservative estimate rounds out this set of possible choices, as it simply seeks to balance a weighted product of the probability and magnitude of error (see Figure N1-1, which gives examples of what purpose each estimator serves). Thus, the choice of risk assessment estimates can certainly be explicit, and can and should be unbiased in the sense of deriving from an open and honest process, but it *cannot* be wholly objective or value-neutral. Because leaving EPA with no principle for choosing among these estimators would itself be a value-laden decision, some members of the committee have advocated "plausible conservatism," cognizant that this is an *alternative* judgment.
- *Science*. The tendency of critics of our position to hold up terms such as "best science" or "credible science" as the alternative should not confuse readers into inferring that any alternatives must espouse "bad science" or "incredible science." Defaults which are not credible have no place in either of the proposals advocated in these appendices. Supporters of "plausible conservatism" believe defaults based on this principle have additional merits beyond their credibility, and that "best science" ought to be more than data for data's sake or anti-conservatism for its own sake. Looking to the future, none of the members of the committee wishes to "freeze" risk assessment science in its current incarnation, or to suppress information about new scientific ideas that challenge existing ones. The intelligent question is not *whether* to improve the science, but *how* and *when* to include it in risk characterization for risk management. Again, in

the vexing paradigm case where an alternative model incompatible with the default predicts vastly smaller or zero risk, the operational decision involves whether to leap to the new risk characterization, to develop a hybrid of the two theories, or to proceed cautiously until general scientific consensus supports the alternative. This section of the chapter has explored reasons why the last alternative is preferable, and if thoughtfully implemented, will fuel rather than freeze scientific research.

- *EPA Practice*. As the previous chapter indicates, EPA has always had to walk the fine line between too much flexibility and too much rigidity. Even though the committee is concerned that EPA has not had an underlying rationale for its decisions to this point, on balance some of us feel that its individual decisions to depart from defaults have managed this tension admirably well. We are unaware of serious charges that EPA has been unreceptive to new scientific information; indeed, according to some of the references cited above, even in the methylene chloride and CIGA cases, EPA has arguably been too quick to adopt "new science."
- *Risk Management*. This chapter has explored in some detail the intertwining, rather than the boundary, of risk assessment methodology and risk management practice. None of the suggestions made here violate the principle that risk management concerns should not unduly influence the conduct of risk assessment; they only reinforce the point that risk assessment exists to provide useful answers to the questions risk managers choose to ask. And whatever one thinks about the advisability of a clear attempt to separate risk assessment from risk management, this discussion has shown that a "plausible conservatism" orientation is no more violative of that boundary than a central tendency orientation would or could be. Furthermore, both "plausible conservatism" and the "best science" alternative leave vast room for risk managers to exercise their rightful discretion, particularly in the selection of decision alternatives and the integration of information external to the risk assessment (e.g., cost and efficiency estimates, public concerns) on which real decisions often hinge. Finally, we hope to have dispelled the *false choice* that others have posited between valuing science and the values held by scientists. Surely as scientists or otherwise, our values include respect for public health precaution, for predictably and order, and for striking a thoughtful and appropriate balance between the inevitable errors that uncertainty causes. We could decide that other values outweigh these, but we cannot rationalize such a choice by costuming it in the garb of "good science." "Plausible conservatism" embraces the idea that assessors and managers need not abandon either their valuing of science or their values as scientists. Supporters of this principle hope that EPA will follow this path, even though it is presented here as a recommendation that the full committee could not agree to.

Afterthoughts

The alternative view which follows (Appendix N-2) was written after this Appendix was completed. Together, these two statements reflect reasoned disagreement which I hope will provide EPA with "grist for the mill" to help it resolve important questions about risk assessment principles and model uncertainty. However, there are a number of inconsistencies and misinterpretations in Appendix N-2 that I believe cloud this debate. Some of the ambiguity stems from the lack of responsiveness to important issues raised in this Appendix. For example, Appendix N-2 asserts that "risk managers should not be restricted by value judgments made during risk assessment," but nowhere does it explain how this vision could be realized, in light of the assertions herein that a vague call for "full use of scientific information" must either impose a set of value judgments of its own or else restrict risk assessors to presenting every conceivable interpretation of every model, data set, and observation.[14] Similarly, the statement that "risk characterizations must be as accurate as possible," and the implicit equating of accuracy with the amount of data amassed, responds neither to the assertion that accuracy may not be the most appropriate response to uncertainty nor to the four examples in Appendix N-1 showing that "more science" may lead to less accuracy as well as substitute risk-neutral or risk-prone value judgments for risk-averse ones.

There are legitimate reasons for concern about a principle of "plausible conservatism," concerns that, if anything, might have been strengthened by more specificity in Appendix N-2 about the putative merits of an alternative. But in at least three respects, the material in N-2 misinterprets the stated intent of the "plausible conservatism" proposal, thus making a fair comparison impossible.

(1) Proponents of the "plausible conservatism" approach assuredly do not believe that "the fundamental output of a risk assessment is [or should be] a single estimate of risk: one number." This "red herring" permeates Appendix N-2 despite the clear statements in Appendix N-1 that default options only provide a scaffolding upon which all of the uncertainties and variabilities contingent on the models selected must be assessed and communicated. In fact, Chapter 9 of the report states quite clearly the committee's view that risk assessors must *abandon* their reliance on single point estimates and instead routinely provide quantitative descriptions of uncertainty (preferably via probability distributions). Indeed, three of the four specific recommendations in Appendix N-1 for implementing the "plausible conservatism" proposal reinforce the purpose of Chapter 9

[14] In fact, the Appendix contradicts itself a few pages later when it states that "weighing the plausibility of alternatives is a highly judgmental evaluation that must be carried out by scientists." This is a clear call for scientists to play a role in science policy, which Appendix N-1 clearly *endorses*, but then the authors of N-2 return to the "hands off" view and re-contradict themselves with the admonition that "scientists should not attempt to resolve risk management disputes by influencing the choice of default options."

by emphasizing "the uncertainty distributions that result" from proper risk assessments conducted according to guidelines containing default options.[15] The only uncertainty not accounted for by estimating risk using default models unless there are specific reasons to replace them is the subjective probability that the other model(s) is/are correct. Even though this additional uncertainty may be substantial, the committee agreed in Chapter 9 that at present, both the methodology for coming up with the subjective weights and the theory for how to meaningfully "average" irreconcilable models are sufficiently rudimentary that a single risk characterization covering all plausible models would be a precarious basis for risk management and communication. Thus, however the proposal in Appendix N-1 and Appendix N-2 differ, they do not advocate different "fundamental outputs of risk assessment."

(2) The authors of Appendix N-2 characterize their recommendation that "risk managers can and should override conservative default value judgments in the risk assessment process whenever they believe it is appropriate public policy to do so" as one that "contrasts sharply with the approach advocated by Dr. Finkel." For the record, nothing in Appendix N-1 advocates constraining the activities of risk managers in any such way. Indeed, the last paragraph of Appendix N-1 speaks to the "rightful discretion" risk managers should have to supplement, subordinate, or discard quantitative risk information when they deem this necessary to make sound decisions. If a risk characterization (again, a distribution, not just a number) emerging from the "plausibly conservative" models chosen suggests a significant risk, the manager can still let other concerns (economics, feasibility, equity, or even lack of confidence in the scientific underpinning of the risk assessment) justify not reducing the risk. What proponents of "plausible conservatism" object to, and what Appendix N-2 either leaves open or endorses (it is unclear), is for someone (a scientist? a manager?) to declare as a matter of science that a risk *already is acceptable*, simply because other models may exist that give more sanguine risk predictions than do the conservative defaults.

(3) Despite all their criticism of how even examining "conservatism" intrudes into policy, the authors of Appendix N-2 admit they "do not object to ["plausible conservatism"] for selecting the default options," only to its use in deciding when to displace an option. What justification could make the same principle appropriate at the outset but objectionable from then on? Their stated objection is that it will "freeze risk characterizations at the level determined by

[15] A substantial amount of uncertainty may be contributed by the parameters that drive risk models, even before interindividual variability is taken into account. For example, even if one specifies that the linearized multistage model must be used, the uncertainty in cancer potency due only to random sampling error in the typical bioassay can span five orders of magnitude at a 90 percent confidence level (Guess et al., 1977).

the conservative default options." Appendix N-1, however, argues that consensus processes in science neither intend to nor result in the "freezing" of science, only in "freezing out" unpersuasive or poor-quality science until it improves. It seems, then, that the authors of Appendix N-2 really do object to reliance on prudence and conservatism for the initial selection of the defaults, and only tolerate the existing defaults because of their expectation that they could be abandoned speedily.

In contrast to some of the issues raised above, where there really is less disagreement that Appendix N-2 indicates, here there is more controversy than Appendix N-2 admits to. Our lack of consensus on this most fundamental issue —how to choose and how to modify default options—is what caused the committee to decide not to recommend any principles for meeting these challenges.

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Appendix N-2

Making Full Use of Scientific Information in Risk Assessment

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Introduction

This appendix is written in response to Appendix N-1 written by Adam Finkel, which is included in the CAPRA report at the request of the committee. That appendix advocates a principle of "plausible conservatism" for choosing and altering default assumptions and in making cancer risk estimates. It describes this principle as an alternative to the use of best available science and calculation of central tendency risk estimates. This appendix proposes an alternative view to Appendix N-1. We present a different framing of the issue of making full use of science in risk assessment, as opposed to increasing the use of conservative value judgments as described in Appendix N-1.

EPA already practices what we interpret as plausible conservatism in the selection of default options. As set forth in the 1986 *Guidelines for Carcinogen Risk Assessment*, EPA has selected its default options to be scientifically plausible and protective of human health. EPA's cancer potency estimates are intended to be plausible upper bounds on risk. Neither we nor others on the CAPRA Committee have asserted that these EPA risk assessment procedures are inappropriate. Rather CAPRA has sought to strengthen EPA's risk assessment process through further refinements. One of the potential refinements is an explicit standard for departure from defaults. We have concerns that using plausible conservatism as the standard for departure from defaults, as advocated in Appendix N-1, may not be useful and appropriate.

A major theme of the CAPRA report is that of an iterative approach to risk assessment. EPA should carry out risk assessments at multiple levels, with more detail and more use of site and substance-specific data in the upper tiers of an

iterative process. While simple procedures and single-number estimates are appropriate for screening purposes in lower tiers of risk assessment, explicit disclosure of uncertainty and results from multiple scientifically plausible models are encouraged as part of upper tier risk assessment.

It is assumed in Appendix N-1 that the fundamental output of a risk assessment is a single estimate of risk: one number. We take a very different view, that risk assessment is a process for summarizing the available scientific information in both qualitative and quantitative form, for risk managers and for interested members of the public. Thus, regulatory decisions on managing risks should not be driven solely by single number risk estimates, but rather by a more comprehensive characterization of available scientific information, including uncertainties. We believe the CAPRA report strongly supports this latter interpretation.

An important aspect of risk management is the management of research directed at improving risk assessments by reducing uncertainty, permitting conservative assumptions to be superseded by more accurate models and observational data. The tiered approach to risk assessment and explicit consideration of both model and parameter uncertainties will facilitate identification of the opportunities for research that are most important for achieving the nation's health protection, environmental, and economic goals. We view debate over which conservative assumption to use in risk assessment as a poor substitute for an effective process to identify and pursue research that will improve regulatory decisions by reducing both the uncertainties and the need for the conservative assumptions.

Organization Of This Appendix

In this appendix, we discuss: 1) the role of risk assessment in supporting societal decisions on managing risk; 2) the use of "plausible conservatism" in selecting default options and alternatives to default options; 3) the use of an iterative approach in which specific science displaces default options; 4) the need for risk characterizations to be matched to their intended uses, and why a single quantitative estimate of risk may not be adequate; 5) why the process for conducting science-based risk assessments should be integrated and comprehensive; and 6) how risk assessments can serve an important role in guiding research to improve future risk assessments.

The Role of Risk Assessment in Supporting Societal Decisions on Managing Risk

The development of risk assessments is one part of a larger process by which societal decisions and actions concerning risks are made. Risk assessments are that phase of the overall process in which all of the available information concerning exposure to the agent(s), the agent's(s') ability to cause adverse responses, and exposure-dose-response relationships, is synthesized into a risk

characterization whose degree of comprehensiveness is matched to the intended use of the risk characterization. When specific data are not available, default options based on general scientific knowledge and risk assessment policy are used. The risk characterization product of the risk assessment is then used as input along with a diverse array of other information to make a wide range of risk-based decisions, as for example, whether to limit exposure to the agent(s) (and if so, to what extent). These risk-based decisions may on occasion involve a comparison of risks between agents causing similar adverse responses or, more broadly, disease. In other cases, the risk characterization may be used as input to decisions as to how to allocate economic or other societal resources. Clearly, risk characterizations must be as accurate as possible because of the potential importance of the decisions concerning health (and disease) and allocation of scarce societal resources.

This appendix proposes that risk characterizations should be developed by a well-documented process that makes full use of the available scientific data. When specific data are not available, the process should use default options and other assumptions that are clearly identified. The end-product risk characterization should be reported with a degree of comprehensiveness matched to its intended use and in a form that can be readily understood by decision makers and interested members of the public. One intent of the process is to avoid the introduction of *unidentified* bias that would either under-estimate or over-estimate the risk being characterized. The approach we advocate emphasizes scientific plausibility with regard to the use of alternative models and appropriate disclosure of uncertainties.

The approach we are advocating contrasts sharply with the approach advocated by Dr. Finkel, which introduces into the risk assessment process an additional standard: whether the alternative based on the scientific information yields a plausible, conservative estimate of risk. A default option would be displaced only if it is found to be no longer plausible, or if a plausible alternative gives a higher estimate of risk. Thus, judgments on the extent of conservatism would largely determine the result from the risk assessment process. It is our opinion that value judgments as to the degree of conservatism should not have such a large influence on the output of the risk assessment process. We believe that EPA should make these value judgments consistently according to established guidelines where such judgments are necessary (e.g., choice of default options), and should disclose the use of such judgments fully to risk managers and to the public.

The value judgments are most appropriately dealt with as part of the risk management or risk decision-making phase of the overall process. In particular, risk managers should not be restricted by value judgments made during risk assessment. Risk managers can and should override conservative default value judgments in the risk assessment process whenever they believe it is appropriate public policy to do so. Such departures should be clearly identified as policy and not as science. Risk managers must assume full responsibility for making such

overrides and for explaining their reasoning to the interested and affected members of the public.

Use of "Plausible Conservatism" in Selecting Default Options and Alternatives to Default Options

It has been noted that inference guidelines, or default options as they are typically called in this report, are generic guidelines used when the necessary scientific information is not available. These guidelines are based on general scientific knowledge and applied to assure consistency in the development of multiple risk assessments. It is our understanding that EPA has selected default options that are scientifically plausible and conservative in the sense that they are intended to avoid underestimating health risks. Hence, these generic guidelines generally follow the principle of "plausible conservatism" as we believe it is described in Appendix N-1. We do not object to this approach for selecting the default options.

We do object to the use of "plausible conservatism" as a criterion in deciding when specific science can be used to replace a default option. The use of "plausible conservatism" as the test for displacing default options places an excessively high hurdle for the new science. The use of "plausible conservatism" will therefore discourage the conduct of research to generate the scientific information that might displace the use of the default option. The result will be to freeze risk characterizations at the level determined by the conservative default options.

As specific science is developed and used to replace default options, the result will typically be a reduction both in the estimates of risk and the extent of uncertainty in the risk estimates. The replacement of default options with specific science was illustrated in Chapter 6 using formaldehyde as an example. In this case the initial risk estimate, which was based on a default option for relating exposure to response, i.e., the cancer risk, had a plausible upper bound estimate of 0.016 (1.6×10^{-2}) at 1 ppm. The lower limit may be zero. Thus, there was a wide range of uncertainty, from 0 to 0.016. In successive iterations as new scientific information was incorporated on delivered dose to target tissue using data on DNA-protein cross-links, first from rats and then from monkeys, the upper bound on risk at 1 ppm was reduced to 2.8×10^{-3} and then to 3.3×10^{-4}. For neither of these iterations can a lower bound estimate of zero be excluded. Thus, at the last iteration the range of uncertainty has been reduced to 0 to 3.3×10^{-4}. This is a substantial reduction from the 0 to 1.6×10^{-2} calculated based on the default options.

In this example the departure from the default options was far more plausible than the original default options. The DNA-protein cross-links provide a direct measurement of a biomarker for the extent to which the formaldehyde is penetrating into tissues where cancers might be induced.

In many other situations, the difference in plausibility between the default and the alternative using specific scientific information may be less apparent. It is our judgment that weighing the plausibility of alternatives is a highly judgmental evaluation that must be carried out by scientists. We believe it would be a mistake to try to define a sharp threshold for plausibility. Such a sharp threshold will stifle research and impede communication about uncertainties. When an alternative approach is judged plausible, but the default option also plausible, it will be appropriate for the risk estimates from both approaches to be conveyed to the risk manager, as CAPRA has recommended.

Better criteria for departures from defaults are needed. However, we believe that scientific judgment will remain at the heart of the process for determining that a default option should be displaced, either for a specific substance, or for a class of substances. Chapter 6 provides several examples of instances in which departures from defaults have been accepted, or considered and rejected as not yet adequately supported by scientific information, based on outside scientific peer review through the EPA Science Advisory Board. In our opinion EPA's process for making such judgments works reasonably well—although there is clearly room for improvement. More research directed at the important uncertainties should permit more departures from defaults, based upon adequate support from the scientific information obtained through the research.

We view the extent of conservatism in risk assessment guidelines as a policy issue to be determined by EPA, most appropriately through notice and comment rulemaking in the same manner as when EPA risk assessment guidelines were adopted in 1986. The proposal in Appendix N-1 does not give precise guidance for establishing default options or for departing from these defaults. Scientists may disagree as to whether a model is plausible or not plausible, and lack of plausibility will be very difficult to establish outside the range of observed data. The usual choice will be between simple models whose structure is assumed, (e.g., low dose linearity) vs. more complex models based on knowledge of biological and pathobiological processes. Both alternatives may be judged plausible. However, the biologically based models may be more valuable because they incorporate more information and provide a better basis for discriminating on the extent of the risk posed by different chemicals at relevant levels of human exposure.

We are also concerned that recommendations from CAPRA on policy issues could be inappropriate and subject to misinterpretation. Therefore, we believe it is inappropriate for the National Research Council to recommend default options to EPA. NRC recommendations might be perceived as being based on solely on science, but such would not be the case; such recommendations would reflect value judgments that scientists are no more qualified to make than other citizens. However, it is appropriate for NRC to point out where default options are needed, so that these policy questions can be addressed by the regulatory agency. For example, should the same cancer potency be used for all chemicals in a class

(discussed at the end of Chapter 6)? Should the same cancer potency be applied to all people, or should sensitive subgroups be treated separately (discussed in Chapter 10)? It is our position that judgments on what are the appropriate defaults should be made by the regulatory agency, and not by the members of an NRC committee.

There are broader questions of risk assessment and risk management policy that CAPRA has declined to address. There is much dispute and inconsistency on the appropriate basis for regulating toxic chemicals, especially carcinogens. Some within the scientific community believe that Congress and the regulatory agencies have gone much too far in regulating some chemicals (e.g., synthetic pesticide residues in processed food) and not far enough in regulating other chemicals (indoor radon and other indoor air toxicants). We believe that such disputes and inconsistencies should be addressed using risk assessment for communication, to inform those with decision responsibility what science can and cannot say about the magnitude of the risks posed by chemicals to health and the environment. Scientists should not attempt to resolve risk management disputes by influencing the choice of default options or the criteria for departure from default options.

The Use of an Iterative Approach, in which Specific Science Displaces Default Options and Provides a Means to Improve Risk Assessments and Reduce Uncertainty in Risks

The CAPRA report advocates the conduct of iterative risk assessments matched to decision-making needs. This approach recognizes that EPA must deal with at least 189 hazardous air pollutants, many with limited data and, perhaps, posing low risks. EPA needs an approach for carrying out iterative risk assessment on hazardous air pollutants, and Chapter 12 builds upon EPA's planned methodology to describe such an approach. As a part of this approach, EPA must develop a system for prioritizing these chemicals so that the limited funds available may be used most effectively to protect human health. Because of differences in the available data and the differences in the magnitude of the risk posed by different chemicals, EPA should not deal with each chemical the same way. The highly quantitative formal techniques described in CAPRA Chapters 9, 10, 11 are not intended for every chemical, but only for supporting the most important and difficult regulatory decisions, for which advanced analytical concepts and procedures may be needed. The sophistication and complexity of these methods add to the difficulty of communicating to regulatory decision makers and to the public. EPA needs a risk assessment process that can deal effectively, cheaply, and quickly with most of the chemicals, while permitting more sophisticated and data-intensive risk assessment in situations where the additional time, expense, analytical sophistication, and risk communication difficulties are warranted by the importance of the regulatory decisions.

Risk Characterizations Must Be as Clear and Comprehensive as Practical, Given Their Intended Uses; and A Single Quantitative Estimate of Risk May Not Be Adequate

The risk assessment process and the resulting risk characterization should be matched to the intended use of the risk characterization. (Recall the discussion in the preceding section of the need for an iterative approach.) Obviously, the degree of comprehensiveness that can be achieved for a given risk characterization will be dependent on the extent of the scientific information available.

For the chemicals with the least amount of data the risk characterization may be a qualitative, narrative summary of the limited available information. For chemicals with more extensive data, such as several bioassays, the risk characterization may include a plausible upper bound risk estimate, using the 95% upper confidence limit computed from the bioassay data set that yields the highest risk estimate (e.g., most sensitive strain, sex, species, and tumor end point) and a conservative and relatively crude exposure estimate.

For the most extensive data sets, it may be possible to provide multiple risk calculations corresponding to alternative models and data sets corresponding to individuals and populations. These data may be organized in the form of one or more probability distributions, from which a probability distribution on risk is computed. The probability distribution on risk may be summarized by using expected values or other summary statistics computed through Monte Carlo analysis or other probabilistic analysis techniques. Such central tendency estimates will be helpful supplements to upper and lower bound calculations (more generally, statistical confidence limits) to assist decision makers and the public in understanding the implications of the probability distributions. Such analysis based on the most extensive available data for cancer potency and exposure has not, to our knowledge, been carried out in support of a major regulatory decision, but the procedures involved are illustrated in Appendices (Texaco and ENSR articles) and in the scientific literature (Wallsten and Whitfield, 1989; Howard et al., 1972).

The proposal in Appendix N-1 for plausible conservatism seems to assume that the output of risk assessment is a single risk number that can be used for regulatory decision making. We oppose this aspect of his proposal, especially for the upper tiers of risk assessment. The goal for risk assessment should be to inform decision makers and the public, not to give them a number.[1] To the

[1] In Appendix N-1, Dr. Finkel uses an example of when to leave for the airport to illustrate his advocacy of conservative estimates, and we use the same example to make the point that single-number estimates may be inadequate as a summary of information for purposes of decision making. The decision on when to leave for the airport depends on the information about how long it will take to get to the airport, an uncertain quantity. It is our judgment that most decision makers would not wish to have this uncertainty summarized as a single estimated travel time, as he has asserted. Rather, we believe that decision makers prefer to have a description of the possibilities and their

extent that risk assessment provides only one number, based on conservative assumptions, then the group that determines which conservative assumptions shall be used will determine regulatory policy. Thus, the discretion of the risk manager will be preempted by the risk assessment process.

The EPA Science Advisory Board Report on Dioxins (EPA, 1989) stressed the importance of replacing linear extrapolation with a biologically based model, and that the default of linearity might cause risk to be overestimated or underestimated. The SAB encouraged EPA to consider revisions in the regulatory standard based on policy and on the scientific uncertainties. SAB did not support changing the single number risk estimate on the basis of the scientific information then available.

It can be argued theoretically that for decision making, the best single number will be the expected value—the average over the probability distribution. However, we believe that the distribution is better than the any single number. If an average value is to be used, misinterpretation should be minimized, and for more than a decade EPA's risk estimates have generally been upper bounds. (Only a few risk estimates based on human epidemiology have represented conceptual departures—for example, lung cancer from indoor radon, where the health risk estimate comes from extrapolation of observed lung cancer incidence in uranium miners.)

In Appendix N-1, the example of a substance that may pose an unacceptably high risk of X, or zero, depending on which of two incompatible biologic theories is true. Such a situation is clearly one in which risk managers will wish to learn about this critically important uncertainty as to which theory is correct. Within the risk management context if not within risk assessment, it may be useful to characterize the judgment of knowledgeable scientists in terms of a subjective probability. Suppose there is a consensus among scientists that the probability is p that the risk is at or near zero. In our judgment, the decision maker will wish to understand this characterization of the risk: a probability p that the risk is at or near zero and a probability 1-p that the risk is at the high level X. We believe it inappropriate to summarize this situation by presenting only the expected value of (1-p)X as the estimate of risk for the decision maker. The probability distribution should be used for the risk characterization, not one

likelihood. For example, an estimate of the travel time under normal conditions might be supplemented by a description of possible delays and the probabilities that such delays might occur. Such an analysis might be quite simple, with only a few sources of delay considered, or quite complex, requiring a computer to calculate the probability distribution on the time from departure to boarding the airplane. In presenting the analysis, an assessor might highlight the most important uncertainties (e.g., "The normal driving time is approximately 30 minutes, with a probability of 20% that traffic delays might add between 10 and 30 minutes. The probability that travel time by taxi to the airport would exceed one hour is judged to be less than 5%.").

risk estimate. Decision makers and the public should have little difficulty understanding this simple characterization.

The Process for Conducting Science-Based Risk Assessments Should Be Integrated and Comprehensive

The process being advocated for the conduct of science-based risk assessments builds on the general principles outlined in the 1983 NRC Committee Report (the Red Book). We reaffirm these general principles and build on them in proposing a process for the conduct of risk assessments. The general principles we believe to be appropriate include:

- A paradigm linking exposure to dose to response can be used as a structure for integrating data to characterize the risk of a specific pollutant. For characterizing the risk associated with a specific source the paradigm is readily expanded to include a source to exposure linkage.
- Scientific information, to the extent it is available, should be used as much as feasible in the risk assessment process.
- When differences of scientific opinion exist on the use or interpretation of scientific information or hypotheses, these should be clearly documented in the risk assessment process and the impact on risk characterization identified.
- Guidelines are necessary to structure the interpretation and use of scientific information, including consideration of specific scientific information and to guide actions when information is incomplete or absent in particular assessments.
- The guidelines should include clearly identified default options (e.g., the preferred inference option chosen on the basis of risk assessment policy that appears to be the best choice in the absence of data to the contrary).
- Guidelines should promote the use of specific information and departures from the use of default options. Departures from defaults should be based on the scientific validity of the data and models, as judged by scientists.
- All scientific data, scientific assumptions, scientific hypotheses, default options, and the specific risk assessment methodology used should be clearly documented in each risk assessment. Where differences of scientific opinion exist, these differences should be clearly described.
- The resulting risk characterization, including quantitative estimates of risk and probabilistic descriptions of risk, should be communicated to the risk manager in as clear and comprehensive a manner as possible, as appropriate for the intended use of the risk characterization.

Risk Assessments Can Serve an Important Role in Guiding Research to Improve Future Risk Assessments

It is our opinion that risk assessments can have a major role in guiding research to improve the scientific basis for future risk assessments. This will require a new attitude recognizing that the risk assessment process should yield not only a risk characterization but also identify the unanswered questions which, if addressed with research, could have the potential for reducing the uncertainty in the estimates of risk as schematically related in Figure N-1. This process of identifying research needs (opportunities) may be informal or formalized as in the use of sensitivity analyses. Having identified the major sources of uncertainty, the question may be asked as to whether the issue can be addressed with current research technologies and, if so, the potential cost and time required to carry out the research. These costs and time estimates can then be balanced against the potential value of the information in making decisions on proceeding with the targeted research effort.

A recent OTA report, *Researching Health Risks* (OTA, 1993), addressed the issue of conducting targeted research of this kind both as related to specific chemicals but also as a means of improving risk assessment methodology. Obviously, the two go hand-in-hand with research on specific chemicals (in which they serve as useful probes) addressing generic toxicological/risk assessment issues while also providing highly relevant information applicable to the specific chemical.

The most important risk management decisions will involve large potential impacts on public health and large economic consequences from control actions. Such decisions should involve a careful review of the underlying science. Risk managers may wish to consider whether to act with present information, which may involve large uncertainties in the public health consequences, or to delay the decision for a period of time which research is carried out to reduce these uncertainties and therefore provides a better basis for decision. It is our belief that Congress could do much more to encourage EPA, other federal agencies such as NIEHS, and private sector organizations to plan and carry out research to reduce important uncertainties on the health consequences of toxic air contaminants. Such research might take a decade or more to complete, but research started now might provide significant new information supporting departures from defaults that could save billions of dollars in control costs while providing even better protection of public health.

Scientific knowledge of the mechanism by which toxic substances cause cancer and other chronic health impacts is evolving rapidly. However, much of this research is aimed at understanding and treating the health impacts, rather than understanding the relationship of the health impacts to the relatively low levels of exposure to toxic substances in the ambient air. The most important uncertainties are those for which the value of information is high, because resolution

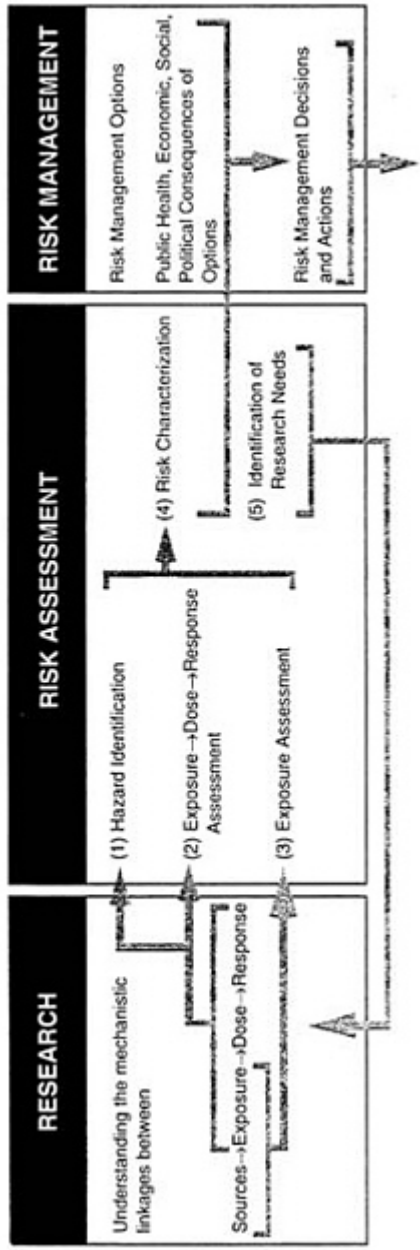

FIGURE N-1 NAS/NRC risk assessment/management paradigm. Source: Adapted from NRC, 1983a.

of the uncertainties are likely to change decisions, leading to substantial benefits in improved public health and reduced control costs (OTA, 1993). More targeted research designed to avoid costly regulations based on conservative default options in risk assessment should pay very large economic dividends, while at the same time allowing better management of the substances that do present substantial risks to public health.

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EPA/540/1-89/002
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Risk Assessment Guidance for Superfund Volume I Human Health Evaluation Manual (Part A)

Interim Final

Office of Emergency and Remedial Response
U.S. Environmental Protection Agency
Washington, D.C. 20450

NOTICE

The policies and procedures set forth here are intended solely as guidance to EPA and other government employees and contractors. This guidance does not constitute rulemaking by the Agency, and cannot be relied on to create a substantive or procedural right enforceable by any party in litigation with the United States. EPA may take action that is at variance with the policies and procedures in this manual and may change them at any time without public notice.

This interim final guidance is based on policies in the proposed revisions to the National Oil and Hazardous Substances Pollution Contingency Plan (NCP), which were published on December 21, 1988 (53 *Federal Register* 51394). The final NCP may adopt policies different than those in this manual and should, when promulgated, be considered the authoritative source. A final version of this manual will be published after the revised NCP is promulgated.

Following the date of its publication, this manual is intended to be used as guidance for all human health risk assessments conducted as part of Superfund remedial investigations and feasibility studies. Issuance of this manual does not invalidate human health risk assessments completed before (or in progress at) the publication date and based on previously released Agency guidance.

ABOUT THE REVISION . . .

WHAT IT IS EPA's *Human Health Evaluation Manual* is a revision of the *Superfund Public Health Evaluation Manual* (SPHEM; October 1986); it is Volume I of the two-volume set called *Risk Assessment Guidance for Superfund*. This manual has three main parts: the baseline risk assessment (Part A); refinement of preliminary remediation goals (Part B); and evaluation of remedial alternatives (Part C). (Only Part A is included in the first distribution; see below.)

WHO IT'S FOR Risk assessors, risk assessment reviewers, remedial project managers (RPMs), and risk managers involved in Superfund site cleanup activities will benefit from this revision.

WHAT'S NEW This revision builds upon the process established in SPHEM and provides more detailed guidance on many of the procedures used to assess health risk. New information and techniques are presented that reflect the extensive Superfund program experience conducting health risk assessments at Superfund sites. Policies established and refined over the years -- especially those resulting from the proposed National Oil and Hazardous Substances Pollution Contingency Plan (NCP) -- have been updated and clarified. Additionally, the links between the human health evaluation, the environmental evaluation, and the remedial investigation/feasibility study (RI/FS) have been strengthened.

In Part A you will find:

For the risk assessor -- Updated procedures and policies, specific equations and variable values for estimating exposure, and a hierarchy of toxicity data sources.

For the risk assessment reviewer -- A baseline risk assessment outline for consistent presentation of risk information and format, and a reviewer's checklist to ensure appropriate quality and content of the risk assessment.

For the RPM -- A comprehensive overview of the risk assessment process in the RI/FS, a checklist for RPM involvement throughout the process, and a complete index for quick reference.

For the risk manager -- An expanded chapter on risk characterization (Chapter 8) to help summarize and present risk information for the decision-maker, and more detailed descriptions of uncertainties in the assessment.

DISTRIBUTION PLAN This manual is being distributed as an interim final document while the proposed NCP is being finalized. After the final NCP is published, the manual will be updated and finalized. Parts B and C -- which were not distributed as interim final because they are highly dependent on possible revisions to the NCP -- will be added. Periodically, updates of portions of the manual will be distributed.

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LIST OF EXHIBITS

PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) requires that actions selected to remedy hazardous waste sites be protective of human health and the environment. CERCLA also mandates that when a remedial action results in residual contamination at a site, future reviews must be planned and conducted to assure that human health and the environment continue to be protected. As part of its effort to meet these and other CERCLA requirements, EPA has developed a set of manuals, together entitled *Risk Assessment Guidance for Superfund*. The *Human Health Evaluation Manual* (Volume I) provides guidance for developing health risk information at Superfund sites, while the *Environmental Evaluation Manual* (Volume II) provides guidance for environmental assessment at Superfund sites. Guidance in both human health evaluation and environmental assessment is needed so that EPA can fulfill CERCLA's requirement to protect human health and the environment.

The *Risk Assessment Guidance for Superfund* manuals were developed to be used in the remedial investigation/feasibility study (RI/FS) process at Superfund sites, although the analytical framework and specific methods described in the manuals may also be applicable to other assessments of hazardous wastes and hazardous materials. These manuals are companion documents to EPA's *Guidance for Conducting Remedial Investigations and Feasibility Studies Under CERCLA* (October 1988), and users should be familiar with that guidance. The two Superfund risk assessment manuals were developed with extensive input from EPA workgroups comprised of both regional and headquarters staff. These manuals are interim final guidance; final guidance will be issued when the revisions proposed in December 1988 to the National Oil and Hazardous Substances Pollution Contingency Plan (NCP) become final.

Although human health risk assessment and environmental assessment are different processes, they share certain common information needs and generally can use some of the same chemical sampling and environmental setting data for a site. Planning for both assessments should begin during the scoping stage of the RI/FS, and site sampling and other data collection activities to support the two assessments should be coordinated. An example of this type of coordination is the sampling and analysis of fish or other aquatic organisms; if done properly, data from such sampling can be used in the assessment of human health risks from ingestion and in the assessment of damages to and potential effects on the aquatic ecosystem.

The two manuals in this set target somewhat different audiences. The *Environmental Evaluation Manual* is addressed primarily to remedial project managers (RPMs) and on-scene coordinators (OSCs), who are responsible for ensuring a thorough evaluation of potential environmental effects at sites. The *Environmental Evaluation Manual* is not a detailed "how-to" type of guidance, and it does not provide "cookbook" approaches for evaluation. Instead, it identifies the kinds of help that RPMs/OSCs are likely to need and where they may find that help. The manual also provides an overall framework to be used in considering environmental effects. An environmental evaluation methods compendium published by EPA's Office of Research and Development, *Ecological Assessments of Hazardous Waste Sites: A Field and Laboratory Reference Document* (EPA/600/3-89/013), is an important reference to be used with the manual.

The *Human Health Evaluation Manual* is addressed primarily to the individuals actually conducting health risk assessments for sites, who frequently are contractors to EPA, other federal agencies, states, or potentially responsible parties. It also is targeted to EPA staff, including those responsible for review and oversight of risk assessments (e.g., technical staff in the regions) and those responsible for ensuring adequate evaluation of human health risks (i.e., RPMs). The *Human Health Evaluation Manual* replaces a previous EPA guidance document, *The Superfund Public Health Evaluation Manual* (October 1986), which should no longer be used. The new manual incorporates lessons learned from application of the earlier manual and addresses a number of issues raised since the earlier manual's publication. Issuance of the new manual does not invalidate human health risk assessments completed before (or in progress at) the publication date.

The *Human Health Evaluation Manual* provides a basic framework for health risk assessment at Superfund sites, as the *Environmental Evaluation Manual* does for environmental assessment. The *Human Health Evaluation Manual* differs, however, by providing more detailed guidance on many of the procedures used to assess health risk. This additional level of detail is possible because of the relatively large body of information, techniques, and guidance available on human health risk assessment and the extensive Superfund program experience conducting such assessments for sites.

Even though the *Human Health Evaluation Manual* is considerably more specific than the *Environmental Evaluation Manual*, it also is not a "cookbook," and proper application of the guidance requires substantial expertise and professional judgment.

ACKNOWLEDGEMENTS

This manual was developed by the Toxics Integration Branch (TIB) of EPA's Office of Emergency and Remedial Response, Hazardous Site Evaluation Division. Linda Cullen provided overall project management, contract supervision, and technical coordination for the project under the direction of Bruce Means, Chief of TIB's Health Effects Program.

The EPA Workgroup (comprised of members listed on the following page) provided valuable input regarding the organization, content, and policy implications of the manual throughout its development. The project manager especially wishes to acknowledge the assistance of the Workgroup Subcommittee Chairpersons: Rebecca Madison, Bruce Means, Sue Norton, Georgia Valaoras, Craig Zamuda, and Larry Zaragoza.

Other significant contributors to the manual included Joan Fisk, Michael Hurd, and Angelo Carasea of the Analytical Operations Branch (Office of Emergency and Remedial Response); Paul White, Anne Sergeant, and Jacqueline Moya of the Exposure Assessment Group (Office of Research and Development); and Barnes Johnson of the Statistical Policy Branch (Office of Policy, Planning, and Evaluation). In addition, many thanks are offered to the more than 60 technical and policy reviewers who provided constructive comments on the document in its final stages of development.

ICF Incorporated provided technical assistance to EPA in support of the development of this manual, under Contract No. 68-01-7389.

Robert Dyer, Chief of the Environmental Studies and Statistics Branch, Office of Radiation Programs, served as project manager for Chapter 10 (Radiation Risk Assessment Guidance), with assistance from staff in the Bioeffects Analysis Branch and the regional Radiation Program Managers. Chapter 10 was prepared by S. Cohen and Associates, Incorporated (SC&A), under Contract No. 68-02-4375.

CHAPTER 1

INTRODUCTION

The Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA, or "Superfund"), establishes a national program for responding to releases of hazardous substances into the environment.[1] The National Oil and Hazardous Substances Pollution Contingency Plan (NCP) is the regulation that implements CERCLA.[2] Among other things, the NCP establishes the overall approach for determining appropriate remedial actions at Superfund sites. The overarching mandate of the Superfund program is to protect human health and the environment from current and potential threats posed by uncontrolled hazardous substance releases, and the NCP echoes this mandate.

To help meet this Superfund mandate, EPA's Office of Emergency and Remedial Response has developed a human health evaluation process as part of its remedial response program. The process of gathering and assessing human health risk information described in this manual is adapted from well-established chemical risk assessment principles and procedures (NAS 1983; CRS 1983; OSTP 1985). It is designed to be consistent with EPA's published risk assessment guidelines (EPA 1984; EPA 1986a-e; EPA 1988a; EPA 1989a) and other Agency-wide risk assessment policy. The *Human Health Evaluation Manual* revises and replaces the *Superfund Public Health Evaluation Manual* (EPA 1986f).[3] It incorporates new information and builds on several years of Superfund program experience conducting risk assessments at hazardous waste sites. In addition, the *Human Health Evaluation Manual* together with the companion *Environmental Evaluation Manual* (EPA 1989b) replaces EPA's 1985 *Endangerment Assessment Handbook*, which should no longer be used (see Section 2.2.1).

The goal of the Superfund human health evaluation process is to provide a framework for developing the risk information necessary to assist decision-making at remedial sites. Specific objectives of the process are to:

- provide an analysis of baseline risks[4] and help determine the need for action at sites;
- provide a basis for determining levels of chemicals that can remain onsite and still be adequately protective of public health;
- provide a basis for comparing potential health impacts of various remedial alternatives; and
- provide a consistent process for evaluating and documenting public health threats at sites.

The human health evaluation process described in this manual is an integral part of the remedial response process defined by CERCLA and the NCP. The risk information generated by the human health evaluation process is designed to be used in the remedial investigation/feasibility study (RI/FS) at Superfund sites. Although risk information is fundamental to the RI/FS and to the remedial response program in general, Superfund site experience has led EPA to balance the need for information with the need to take action at sites quickly and to streamline the remedial process. Revisions proposed to the NCP in 1988 reflect EPA program management principles intended to promote the efficiency and effectiveness of the remedial response process. Chief among these principles is a bias for action. EPA's *Guidance for*

Conducting Remedial Investigations and Feasibility Studies Under CERCLA (EPA 1988b) also was revised in 1988 to incorporate management initiatives designed to streamline the RI/FS process and to make information collection activities during the RI more efficient. The *Risk Assessment Guidance for Superfund*, of which this *Human Health Evaluation Manual* is Volume I,[5] has been developed to reflect the emphasis on streamlining the remedial process. The *Human Health Evaluation Manual* is a companion document to the RI/FS guidance. It provides a basic framework for developing health risk information at Superfund sites and also gives specific guidance on appropriate methods and data to use. Users of the *Human Health Evaluation Manual* should be familiar with the RI/FS guidance, as well as with other guidances referenced throughout later chapters of this manual.

The *Human Health Evaluation Manual* is addressed primarily to the individuals actually conducting human health evaluations for sites (frequently contractors to EPA, other federal agencies, states, or potentially responsible parties). It also is targeted to EPA staff responsible for review and oversight of risk assessments (e.g., technical staff in the regions) and those responsible for ensuring an adequate evaluation of human health risks (i.e., remedial project managers, or RPMs). Although the terms risk assessor and risk assessment reviewer are used in this manual, it is emphasized that they generally refer to teams of individuals in appropriate disciplines (e.g., toxicologists, chemists, hydrologists, engineers). It is recommended that an appropriate team of scientists and engineers be assembled for the human health evaluation at each specific site. It is the responsibility of RPMs, along with the leaders of human health evaluation teams, to match the scientific support they deem appropriate with the resources at their disposal.

Individuals having different levels of scientific training and experience are likely to use the manual in designing, conducting, and reviewing human health evaluations. Because assumptions and judgments are required in many parts of the analysis, the individuals conducting the evaluation are key elements in the process. The manual is not intended to instruct non-technical personnel how to perform technical evaluations, nor to allow professionals trained in one discipline to perform the work of another.

KEY PLAYERS IN SUPERFUND SITE RISK ASSESSMENT/ RISK MANAGEMENT

Risk Assessor. The individual or team of individuals who actually organizes and analyzes site data, develops exposure and risk calculations, and prepares human health evaluation (i.e., risk assessment) reports. Risk assessors for Superfund sites frequently are contractors to EPA, other federal agencies, states, or potentially responsible parties.

Risk Assessment Reviewer. The individual or team of individuals within an EPA region who provides technical oversight and quality assurance review of human health evaluation activities.

Remedial Project Manager (RPM). The individual who manages and oversees all RI/FS activities, including the human health evaluation, for a site. The RPM is responsible for ensuring adequate evaluation of human health risks and for determining the level of resources to be committed to the human health evaluation.

Risk Manager. The individual or group of individuals who serves as primary decision-maker for a site, generally regional Superfund management in consultation with the RPM and members of the technical staff. The identity of the risk manager may differ from region to region and for sites of varying complexity.

The *Human Health Evaluation Manual* admittedly cannot address all site circumstances. Users of the manual must exercise technical and management judgment, and should consult with EPA regional risk assessment contacts and appropriate headquarters staff when encountering unusual or particularly complex technical issues.

The first three chapters of this manual provide background information to help place the human health evaluation process in the context of the Superfund remedial process. This chapter (Chapter 1) summarizes the human health evaluation process during the RI/FS. The three main parts of this process -- baseline risk assessment, refinement of

preliminary remediation goals, and remedial alternatives risk evaluation -- are described in detail in subsequent chapters. Chapter 2 discusses in a more general way the role of risk information in the overall Superfund remedial program by focusing on the statutes, regulations, and guidance relevant to the human health evaluation. Chapter 2 also identifies and contrasts Superfund studies related to the human health evaluation. Chapter 3 discusses issues related to planning for the human health evaluation.

1.1 OVERVIEW OF THE HUMAN HEALTH EVALUATION PROCESS IN THE RI/FS

Section 300.430 of the proposed revised NCP reiterates that the purpose of the remedial process is to implement remedies that reduce, control, or eliminate risks to human health and the environment. The remedial investigation and feasibility study (RI/FS) is the methodology that the Superfund program has established for characterizing the nature and extent of risks posed by uncontrolled hazardous waste sites and for developing and evaluating remedial options. The 1986 amendments to CERCLA reemphasized the original statutory mandate that remedies meet a threshold requirement to protect human health and the environment and that they be cost-effective, while adding new emphasis to the permanence of remedies. Because the RI/FS is an analytical process designed to support risk management decision-making for Superfund sites, the assessment of health and environmental risk plays an essential role in the RI/FS.

This manual provides guidance on the human health evaluation activities that are conducted during the RI/FS. The three basic parts of the RI/FS human health evaluation are:

(1) baseline risk assessment (described in Part A of this manual);

(2) refinement of preliminary remediation goals (Part B); and

(3) remedial alternatives risk evaluation (Part C).

Because these risk information activities are intertwined with the RI/FS, this section describes those activities in the context of the RI/FS process. It relates the three parts of the human health evaluation to the stages of the RI/FS, which are:

- project scoping (before the RI);
- site characterization (RI);
- establishment of remedial action objectives (FS);
- development and screening of alternatives (FS); and
- detailed analysis of alternatives (FS).

Although the RI/FS process and related risk information activities are presented in a fashion that makes the steps appear sequential and distinct, in practice the process is highly interactive. In fact, the RI and FS are conducted concurrently. Data collected in the RI influences the development of remedial alternatives in the FS, which in turn affects the data needs and scope of treatability studies and additional field investigations. The RI/FS should be viewed as a flexible process that can and should be tailored to specific circumstances and information needs of individual sites, not as a rigid approach that must be conducted identically at every site. Likewise, the human health evaluation process described here should be viewed the same way.

Two concepts are essential to the phased RI/FS approach. First, initial data collection efforts develop a general understanding of the site. Subsequent data collection effort focuses on filling previously unidentified gaps in the understanding of site characteristics and gathering information necessary to evaluate remedial alternatives. Second, key data needs should be identified as early in the process as possible to ensure that data collection is always directed toward providing information relevant to selection of a remedial action. In this way, the overall site characterization

effort can be continually scoped to minimize the collection of unnecessary data and maximize data quality.

The RI/FS provides decision-makers with a technical evaluation of the threats posed at a site, a characterization of the potential routes of exposure, an assessment of remedial alternatives (including their relative advantages and disadvantages), and an analysis of the trade-offs in selecting one alternative over another. EPA's interim final *Guidance for Conducting Remedial Investigations and Feasibility Studies under CERCLA* (EPA 1988b) provides a detailed structure for the RI/FS. The RI/FS guidance provides further background that is helpful in understanding the place of the human health evaluation in the RI/FS process. The role that risk information plays in these stages of the RI/FS is described below; additional background can be found in the RI/FS guidance and in a summary of the guidance found in Chapter 2. Exhibit 1-1 illustrates the RI/FS process, showing where in the process risk information is gathered and analyzed.

1.1.1 PROJECT SCOPING

The purpose of project scoping is to define more specifically the appropriate type and extent of investigation and analysis that should be undertaken for a given site. During scoping, to assist in evaluating the possible impacts of releases from the site on human health and the environment, a conceptual model of the site should be established, considering in a qualitative manner the sources of contamination, potential pathways of exposure, and potential receptors. (Scoping is also the starting point for the risk assessment, during which exposure pathways are identified in the conceptual model for further investigation and quantification.)

PROJECT SCOPING

Program experience has shown that scoping is a very important step for the human health evaluation process, and both the health and environmental evaluation teams need to get involved in the RI/FS during the scoping stage. Planning for site data collection activities is necessary to focus the human health evaluation (and environmental evaluation) on the minimum amount of sampling information in order to meet time and budget constraints, while at the same time ensuring that enough information is gathered to assess risks adequately. (See Chapter 3 for information on planning the human health evaluation.)

The preliminary characterization during project scoping is initially developed with readily available information and is refined as additional data are collected. The main objectives of scoping are to identify the types of decisions that need to be made, to determine the types (including quantity and quality) of data needed, and to design efficient studies to collect these data. Potential site-specific modeling activities should be discussed at initial scoping meetings to ensure that modeling results will supplement the sampling data and effectively support risk assessment activities.

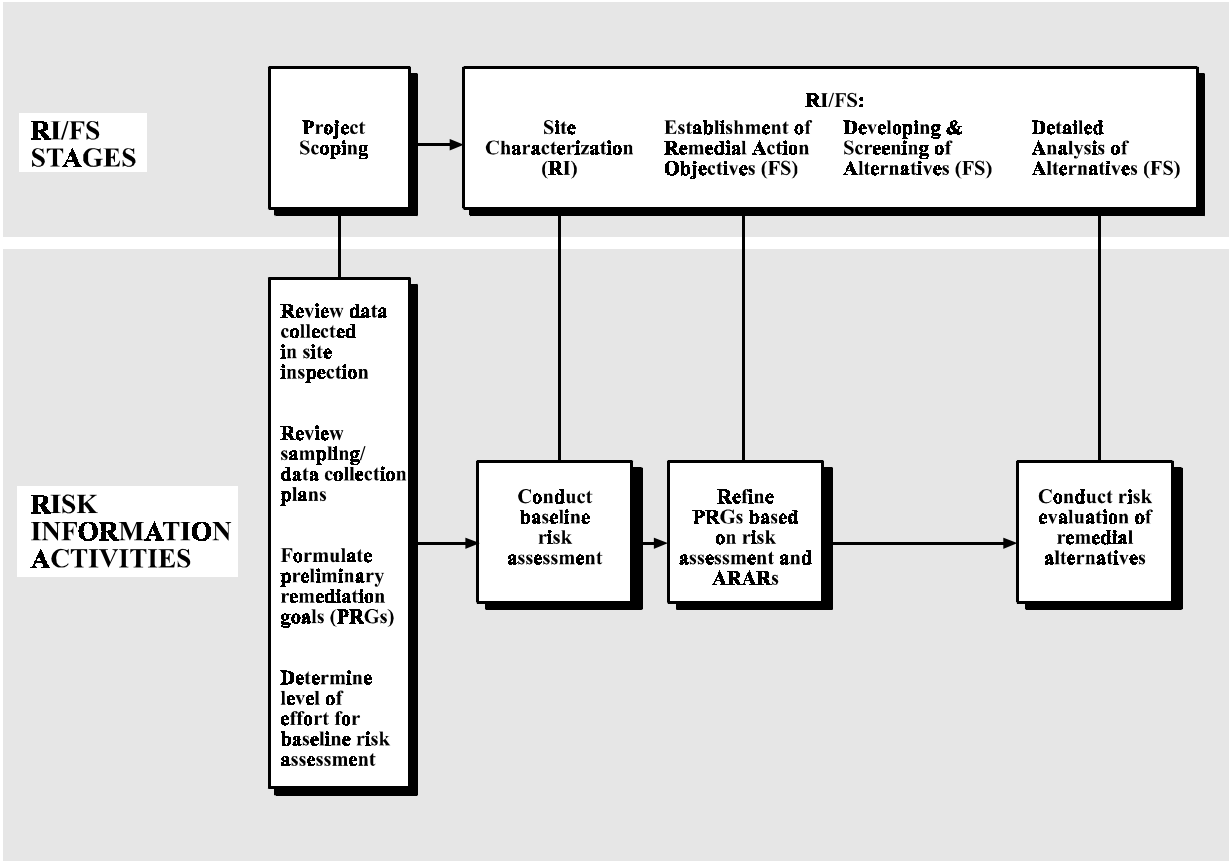
1.1.2 SITE CHARACTERIZATION (RI)

During site characterization, the sampling and analysis plan developed during project scoping is implemented and field data are collected and analyzed to determine the nature and extent of threats to human health and the environment posed by a site. The major components of site characterization are:

- collection and analysis of field data to characterize the site;
- development of a baseline risk assessment for both potential human health effects and potential environmental effects; and
- treatability studies, as appropriate.

Part of the human health evaluation, the baseline risk assessment (Part A of this manual) is an analysis of the potential adverse health effects (current or future) caused by hazardous substance releases from a site in the absence of any actions to control or mitigate these releases (i.e., under an assumption of no action). The baseline risk assessment contributes to the site characterization

EXHIBIT 1-1
RISK INFORMATION ACTIVITIES IN THE RI/FS PROCESS



and subsequent development, evaluation, and selection of appropriate response alternatives. The results of the baseline risk assessment are used to:

- help determine whether additional response action is necessary at the site;
- modify preliminary remediation goals;
- help support selection of the "no-action" remedial alternative, where appropriate; and
- document the magnitude of risk at a site, and the primary causes of that risk.

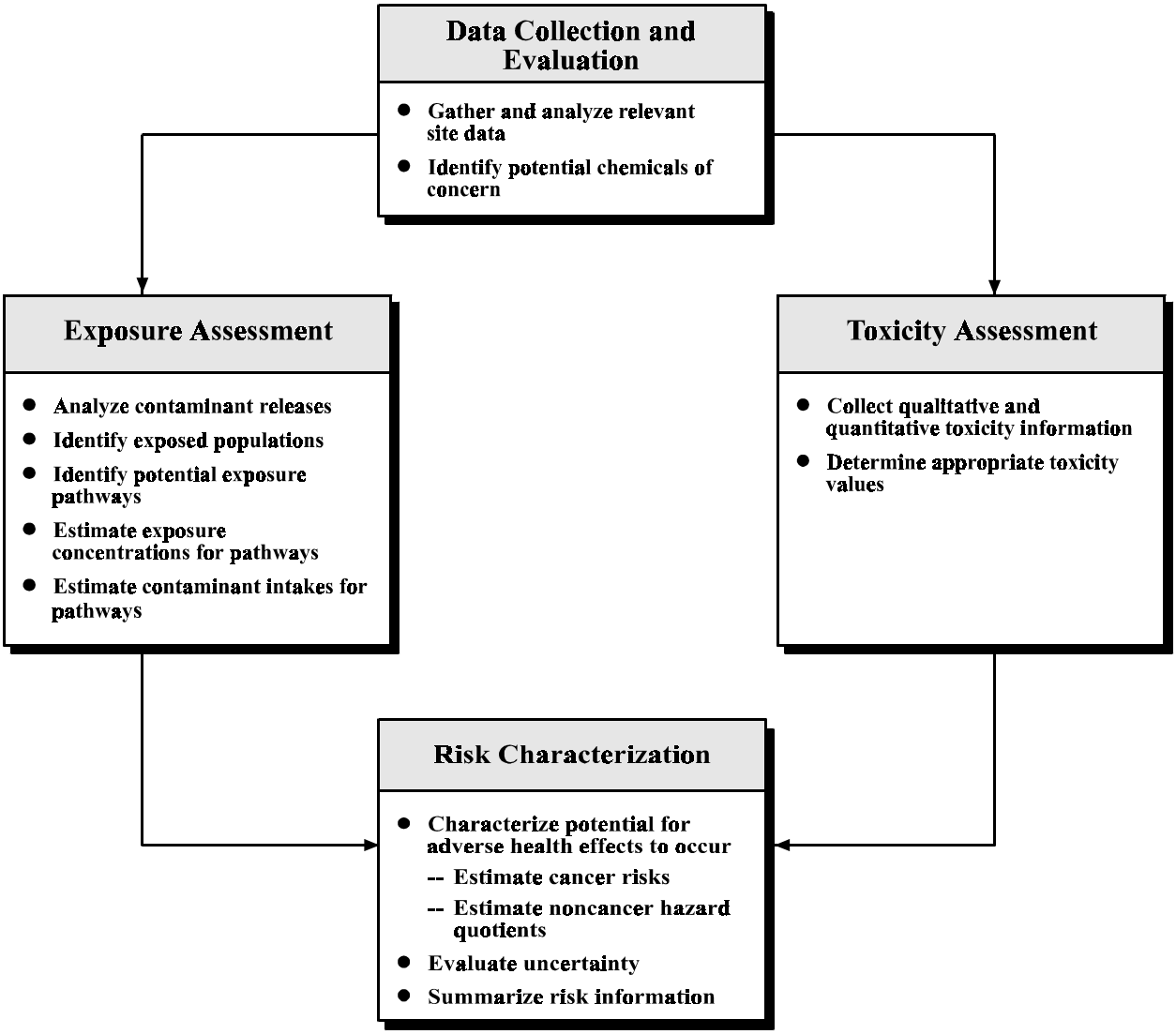
Baseline risk assessments are site-specific and therefore may vary in both detail and the extent to which qualitative and quantitative analyses are used, depending on the complexity and particular circumstances of the site, as well as the availability of applicable or relevant and appropriate requirements (ARARs) and other criteria, advisories, and guidance. After an initial planning stage (described more fully in Chapter 3), there are four steps in the baseline risk assessment process: data collection and analysis; exposure assessment; toxicity assessment; and risk characterization. Each step is described briefly below and presented in Exhibit 1-2.

Data collection and evaluation involves gathering and analyzing the site data relevant to the human health evaluation and identifying the substances present at the site that are the focus of the risk assessment process. (Chapters 4 and 5 address data collection and evaluation.)

An exposure assessment is conducted to estimate the magnitude of actual and/or potential human exposures, the frequency and duration of these exposures, and the pathways by which humans are potentially exposed. In the exposure assessment, reasonable maximum estimates of exposure are developed for both current and future land-use assumptions. Current exposure estimates are used to determine whether a threat exists based on existing exposure conditions at the site. Future exposure estimates are used to provide decision-makers with an understanding of potential future exposures and threats and include a qualitative estimate of the likelihood of such exposures occurring. Conducting an exposure assessment involves analyzing contaminant releases; identifying exposed populations; identifying all potential pathways of exposure; estimating exposure point concentrations for specific pathways, based both on environmental monitoring data and predictive chemical modeling results; and estimating contaminant intakes for specific pathways. The results of this assessment are pathway-specific intakes for current and future exposures to individual substances. (Chapter 6 addresses exposure assessment.)

The toxicity assessment component of the Superfund baseline risk assessment considers: (1) the types of adverse health effects associated with chemical exposures; (2) the relationship between magnitude of exposure and adverse effects; and (3) related uncertainties such as the weight of evidence of a particular chemical's carcinogenicity in humans. Typically, the Superfund site risk assessments rely heavily on existing toxicity information developed on specific chemicals. Toxicity assessment for contaminants found at Superfund sites is generally accomplished in two steps: hazard identification and dose-response assessment. The first step, hazard identification, is the process of determining whether exposure to an agent can cause an increase in the incidence of an adverse health effect (e.g., cancer, birth defect). Hazard identification also involves characterizing the nature and strength of the evidence of causation. The second step, dose-response evaluation, is the process of quantitatively evaluating the toxicity information and characterizing the relationship between the dose of the contaminant administered or received and the incidence of adverse health effects in the exposed population. From this quantitative dose-response relationship, toxicity values are derived that can be used to estimate the incidence of adverse effects occurring in humans at different exposure levels. (Chapter 7 addresses toxicity assessment.)

EXHIBIT 1-2
PART A: BASELINE RISK ASSESSMENT



The risk characterization summarizes and combines outputs of the exposure and toxicity assessments to characterize baseline risk, both in

quantitative expressions and qualitative statements. During risk characterization, chemical-specific toxicity information is compared against both measured contaminant exposure levels and those levels predicted through fate and transport modeling to determine whether current or future levels at or near the site are of potential concern. (Chapter 8 addresses risk characterization.)

The level of effort required to conduct a baseline risk assessment depends largely on the complexity of the site. In situations where the results of the baseline risk assessment indicate that the site poses little or no threat to human health or the environment and that no further (or limited) action will be necessary, the FS should be scaled-down as appropriate.

The documents developed during site characterization include a brief preliminary site characterization summary and the draft RI report, which includes either the complete baseline risk assessment report or a summary of it. The preliminary site characterization summary may be used to assist in identification of ARARs and may provide the Agency for Toxic Substances and Disease Registry (ATSDR) with the data necessary to prepare its health assessment (different from baseline risk assessment or other EPA human health evaluation activities; see Chapter 2). The draft RI report is prepared after the completion of the baseline risk assessment, often along with the draft FS report.

1.1.3 FEASIBILITY STUDY

The purpose of the feasibility study is to provide the decision-maker with an assessment of remedial alternatives, including their relative strengths and weaknesses, and the trade-offs in selecting one alternative over another. The FS process involves developing a reasonable range of alternatives and analyzing these alternatives in detail using nine evaluation criteria. Because the RI and FS are conducted concurrently, this development and analysis of alternatives is an interactive process in which potential alternatives and remediation goals are continually refined as additional information from the RI becomes available.

Establishing protective remedial action objectives. The first step in the FS process involves developing remedial action objectives that address contaminants and media of concern, potential exposure pathways, and preliminary remediation goals. Under the proposed revised NCP and the interim RI/FS guidance, preliminary remediation goals typically are formulated first during project scoping or concurrent with initial RI activities (i.e., prior to completion of the baseline risk assessment). The preliminary remediation goals are therefore based initially on readily available chemical-specific ARARs (e.g., maximum contaminant levels (MCLs) for drinking water). Preliminary remediation goals for individual substances are refined or confirmed at the conclusion of the baseline risk assessment (Part B of this manual addresses the refinement of preliminary remediation goals). These refined preliminary remediation goals are based both on risk assessment and on chemical-specific ARARs. Thus, they are intended to be protective and to comply with ARARs. The analytical approach used to develop these refined goals involves:

- identifying chemical-specific ARARs;
- identifying levels based on risk assessment where chemical-specific ARARs are not available or situations where multiple contaminants or multiple exposure pathways make ARARs not protective;
- identifying non-substance-specific goals for exposure pathways (if necessary); and
- determining a refined preliminary remediation goal that is protective of human health for all substance/exposure pathway combinations being addressed.

Development and screening of alternatives. Once remedial action objectives have been developed, general response actions, such as treatment, containment, excavation, pumping, or other actions that may be taken to satisfy those objectives should be developed. In the process of

developing alternatives for remedial action at a site, two important activities take place. First, volumes or areas of waste or environmental media that need to be addressed by the remedial action are determined by information on the nature and extent of contamination, ARARs, chemical-specific environmental fate and toxicity information, and engineering analyses. Second, the remedial action alternatives and associated technologies are screened to identify those that would be effective for the contaminants and media of interest at the site. The information developed in these two activities is used in assembling technologies into alternatives for the site as a whole or for a specific operable unit.

The Superfund program has long permitted remedial actions to be staged through multiple operable units. Operable units are discrete actions that comprise incremental steps toward the final remedy. Operable units may be actions that completely address a geographical portion of a site or a specific site problem (e.g., drums and tanks, contaminated ground water) or the entire site. Operable units include interim actions (e.g., pumping and treating of ground water to retard plume migration) that must be followed by subsequent actions to fully address the scope of the problem (e.g., final ground-water operable unit that defines the remediation goals and restoration timeframe). Such operable units may be taken in response to a pressing problem that will worsen if unaddressed, or because there is an opportunity to undertake a limited action that will achieve significant risk reduction quickly. The appropriateness of dividing remedial actions into operable units is determined by considering the interrelationship of site problems and the need or desire to initiate actions quickly. To the degree that site problems are interrelated, it may be most appropriate to address the problems together. However, where problems are reasonably separable, phased responses implemented through a sequence of operable units may promote more rapid risk reduction.

In situations where numerous potential remedial alternatives are initially developed, it may be necessary to screen the alternatives to narrow the list to be evaluated in detail. Such screening aids in streamlining the feasibility study while ensuring that the most promising alternatives are being considered.

Detailed analysis of alternatives. During the detailed analysis, each alternative is assessed against specific evaluation criteria and the results of this assessment arrayed such that comparisons between alternatives can be made and key trade-offs identified. Nine evaluation criteria, some of which are related to human health evaluation and risk, have been developed to address statutory requirements as well as additional technical and policy considerations that have proven to be important for selecting among remedial alternatives. These evaluation criteria, which are identified and discussed in the interim final RI/FS guidance, serve as the basis for conducting the detailed analyses during the FS and for subsequently selecting an appropriate remedial action. The nine evaluation criteria are as follows:

(1) overall protection of human health and the environment;
(2) compliance with ARARs (unless waiver applicable);
(3) long-term effectiveness and permanence;
(4) reduction of toxicity, mobility, or volume through the use of treatment;
(5) short-term effectiveness;
(6) implementability;
(7) cost;
(8) state acceptance; and
(9) community acceptance.

Risk information is required at the detailed analysis stage of the RI/FS so that each alternative can be evaluated in relation to the relevant NCP remedy selection criteria.

The detailed analysis must, according to the proposed NCP, include an evaluation of each alternative against the nine criteria. The first two criteria (i.e., overall protectiveness and compliance with ARARs) are threshold determinations and must be met before a remedy can be selected. Evaluation of the overall protectiveness of an alternative during the RI/FS should focus on how a specific alternative achieves protection over time and how site risks are reduced.

The next five criteria (numbers 3 through 7) are primary balancing criteria. The last two (numbers 8 and 9) are considered modifying criteria, and risk information does not play a direct role in the analysis of them. Of the five primary balancing criteria, risk information is of particular importance in the analysis of effectiveness and permanence. Analysis of long-term effectiveness and permanence involves an evaluation of the results of a remedial action in terms of residual risk at the site after response objectives have been met. A primary focus of this evaluation is the effectiveness of the controls that will be applied to manage risk posed by treatment residuals and/or any untreated wastes that may be left on the site, as well as the volume and nature of that material. It should also consider the potential impacts on human health and the environment should the remedy fail. An evaluation of short-term effectiveness addresses the impacts of the alternative during the construction and implementation phase until remedial response objectives will be met. Under this criterion, alternatives should be evaluated with respect to the potential effects on human health and the environment during implementation of the remedial action and the length of time until protection is achieved.

1.2 OVERALL ORGANIZATION OF THE MANUAL

The next two chapters present additional background material for the human health evaluation process. Chapter 2 discusses statutes, regulations, guidance, and studies relevant to the Superfund human health evaluation. Chapter 3 discusses issues related to planning for the human health evaluation. The remainder of the manual is organized by the three parts of the human health evaluation process:

- the baseline risk assessment is covered in Part A of the manual (Chapters 4 through 10);
- refinement of preliminary remediation goals is covered in Part B of the manual (not included as part of this interim final version); and
- the risk evaluation of remedial alternatives is covered in Part C of the manual (not included as part of this interim final version).

Chapters 4 through 8 provide detailed technical guidance for conducting the steps of a baseline risk assessment, and Chapter 9 provides documentation and review guidelines. Chapter 10 contains additional guidance specific to baseline risk assessment for sites contaminated with radionuclides. Sample calculations, sample table formats, and references to other guidance are provided throughout the manual. All material is presented both in technical terms and in simpler text. It should be stressed that the manual is intended to be comprehensive and to provide guidance for more situations than usually are relevant to any single site. Risk assessors need not use those parts of the manual that do not apply to their site.

Each chapter in Part A includes a glossary of acronyms and definitions of commonly used terms. The manual also includes two appendices: Appendix A provides technical guidance for making absorption adjustments and Appendix B is an index.

ENDNOTES FOR CHAPTER 1

1. References made to CERCLA throughout this document should be interpreted as meaning "CERCLA, as amended by the Superfund Amendments and Reauthorization Act of 1986 (SARA)."

2. 40 CFR Part 300. Proposed revisions to the NCP were published on December 21, 1988 (53 Federal Register 51394).

3. The term "public health evaluation" was introduced in the previous risk assessment guidance (EPA 1986f) to describe the assessment of chemical releases from a site and the analysis of public health threats resulting from those releases, and Superfund site risk assessment studies often are referred to as public health evaluations, or PHEs. The term "PHE" should be replaced by whichever of the three parts of the revised human health evaluation process is appropriate: "baseline risk assessment," "documentation of preliminary remediation goals," or "risk evaluation of remedial alternatives."

4. Baseline risks are risks that might exist if no remediation or institutional controls were applied at a site.

5. Volume II of the *Risk Assessment Guidance for Superfund* is the *Environmental Evaluation Manual* (EPA 1989b), which provides guidance for the analysis of potential environmental (i.e., not human health) effects at sites.

REFERENCES FOR CHAPTER 1

Congressional Research Service (CRS), Library of Congress. 1983. *A Review of Risk Assessment Methodologies*. Washington, D.C.

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CHAPTER 2

STATUTES, REGULATIONS, GUIDANCE, AND STUDIES RELEVANT TO THE HUMAN HEALTH EVALUATION

This chapter briefly describes the statutes, regulations, guidance, and studies related to the human health evaluation process. The descriptions focus on aspects of these documents most relevant to human health evaluations and show how recent revisions to the documents bear upon the human health evaluation process. Section 2.1 describes the following documents that govern the human health evaluation:

- the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA, or Superfund) and the Superfund Amendments and Reauthorization Act of 1986 (SARA);
- the National Oil and Hazardous Substances Pollution Contingency Plan (National Contingency Plan, or NCP);
- Guidance for Conducting Remedial Investigations and Feasibility Studies Under CERCLA (RI/FS guidance);
- CERCLA Compliance with Other Laws Manual (ARARs guidance); and
- Superfund Exposure Assessment Manual (SEAM).

Exhibit 2-1 shows the relationship of these statutes, regulations, and guidances governing human health evaluation. In addition, Section 2.2 identifies and briefly describes other Superfund studies related to, and sometimes confused with, the RI/FS human health evaluation. The types of studies discussed are:

- endangerment assessments;
- ATSDR health assessments; and
- ATSDR health studies.

2.1 STATUTES, REGULATIONS, AND GUIDANCE GOVERNING HUMAN HEALTH EVALUATION

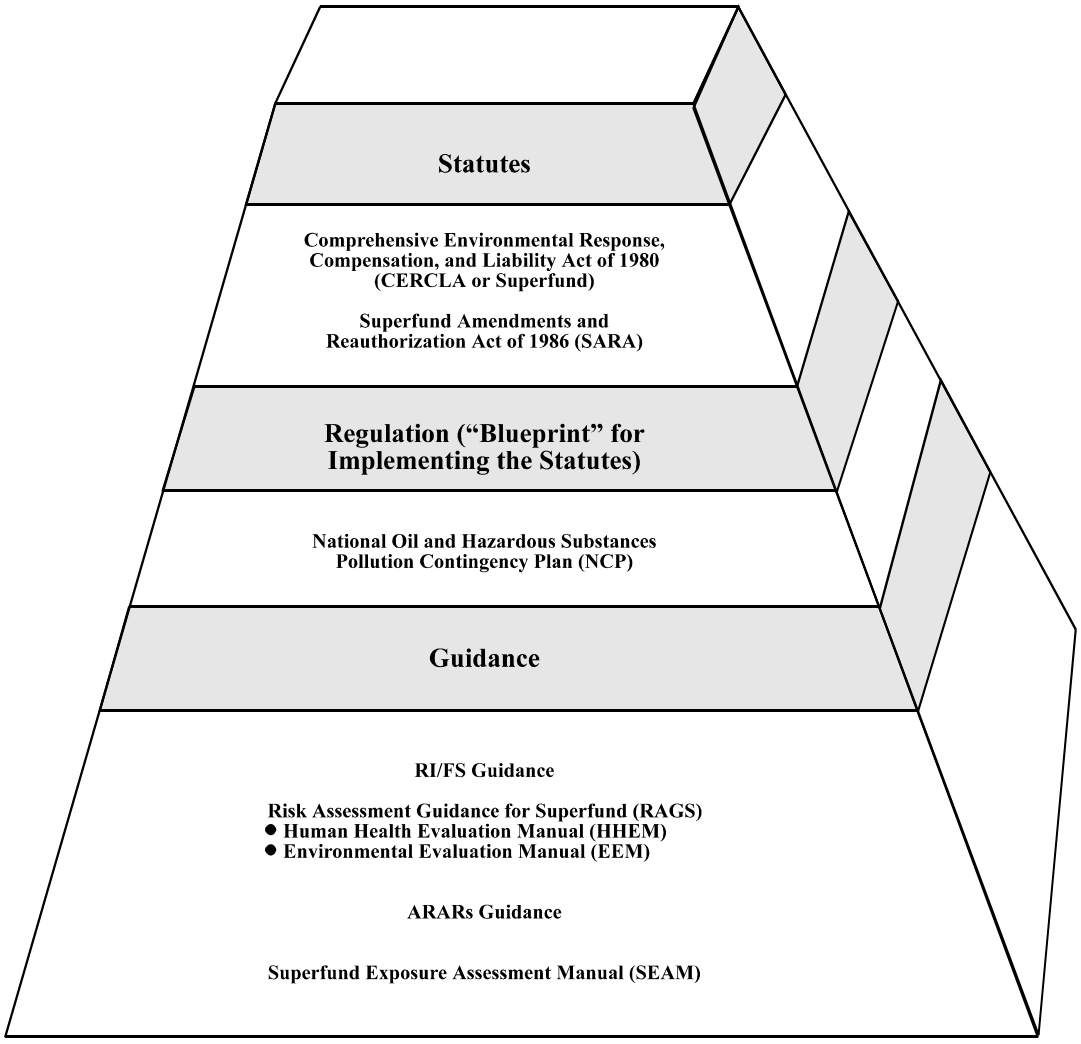
This section describes the major Superfund laws and program documents relevant to the human health evaluation process.

2.1.1 CERCLA AND SARA

In 1980, Congress enacted the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) (42 U.S.C. 9601 et seq.), commonly called Superfund, in response to the dangers posed by sudden or otherwise uncontrolled releases of hazardous substances, pollutants, or contaminants into the

EXHIBIT 2-1

RELATIONSHIP OF DOCUMENTS GOVERNING HUMAN HEALTH EVALUATION



environment. CERCLA authorized $1.6 billion over five years for a comprehensive program to clean up the worst abandoned or inactive waste sites in the nation. CERCLA funds used to establish and administer the cleanup program are derived primarily from taxes on crude oil and 42 different commercial chemicals.

The reauthorization of CERCLA is known as the Superfund Amendments and Reauthorization Act (SARA), and was signed by the President on October 17, 1986. (All further references to CERCLA in this appendix should be interpreted as "CERCLA as amended by SARA.") These amendments provided $8.5 billion for the cleanup program and an additional $500 million for cleanup of leaks from underground storage tanks. Under SARA, Congress strengthened EPA's mandate to focus on permanent cleanups at Superfund sites, involve the public in decision processes at sites, and encourage states and federally recognized Indian tribes to actively participate as partners with EPA to address these sites. SARA expanded EPA's research, development (especially in the area of alternative technologies), and training responsibilities. SARA also strengthened EPA's enforcement authority. The changes to CERCLA sections 104 (Response Authorities) and 121 (Cleanup Standards) have the greatest impact on the RI/FS process.

Cleanup standards. Section 121 (Cleanup Standards) states a strong preference for remedies that are highly reliable and provide long-term protection. In addition to the requirement for remedies to be both protective of human health and the environment and cost-effective, other remedy selection considerations in section 121(b) include:

- a preference for remedial actions that employ (as a principal element of the action) treatment that permanently and significantly reduces the volume, toxicity, or mobility of hazardous substances, pollutants, and contaminants;

- offsite transport and disposal without treatment as the least favored alternative where practicable treatment technologies are available; and

- the need to assess the use of alternative treatment technologies or resource recovery technologies and use them to the maximum extent practicable.

Section 121(c) of CERCLA requires a periodic review of remedial actions, at least every five years after initiation, for as long as hazardous substances, pollutants, or contaminants that may pose a threat to human health or the environment remain at the site. If during a five-year review it is determined that the action no longer protects human health and the environment, further remedial actions will need to be considered.

Section 121(d)(2)(A) of CERCLA incorporates into law the CERCLA Compliance Policy, which specifies that Superfund remedial actions meet any federal standards, requirements, criteria, or limitations that are determined to be legally applicable or relevant and appropriate requirements (i.e., ARARs). Also included is the new provision that state ARARs must be met if they are more stringent than federal requirements. (Section 2.1.4 provides more detail on ARARs.)

Health-related authorities. Under CERCLA section 104(i)(6), the Agency for Toxic Substances and Disease Registry (ATSDR) is required to conduct a health assessment for every site included or proposed for inclusion on the National Priorities List. The ATSDR health assessment, which is fairly qualitative in nature, should be distinguished from the EPA human health evaluation, which is more quantitative. CERCLA section 104(i)(5)(F) states that:

> the term "health assessments" shall include preliminary assessments of the potential risk to human health posed by individual sites and facilities, based on such factors as the nature and extent of contamination, the existence of potential pathways of human exposure (including ground or surface water contamination, air emissions, and food chain contamination), the size and potential susceptibility of the community within the likely pathways of exposure, the comparison of expected human exposure levels to the short-term and long-term health effects associated with identified hazardous substances and any available recommended exposure or tolerance limits for

such hazardous substances, and the comparison of existing morbidity and mortality data on diseases that may be associated with the observed levels of exposure. The Administrator of ATSDR shall use appropriate data, risk assessments, risk evaluations and studies available from the Administrator of EPA.

There are purposeful differences between an ATSDR health assessment and traditional risk assessment. The health assessment is usually qualitative, site-specific, and focuses on medical and public health perspectives. Exposures to site contaminants are discussed in terms of especially sensitive populations, mechanisms of toxic chemical action, and possible disease outcomes. Risk assessment, the framework of the EPA human health evaluation, is a characterization of the probability of adverse effects from human exposures to environmental hazards. In this context, risk assessments differ from health assessments in that they are quantitative, chemical-oriented characterizations that use statistical and biological models to calculate numerical estimates of risk to health. However, both health assessments and risk assessments use data from human epidemiological investigations, when available, and when human toxicological data are unavailable, rely on the results of animal toxicology studies.

2.1.2 NATIONAL CONTINGENCY PLAN (NCP)

The National Contingency Plan provides the organizational structure and procedures for preparing for and responding to discharges of oil and releases of hazardous substances, pollutants, and contaminants. The NCP is required by section 105 of CERCLA and by section 311 of the Clean Water Act. The current NCP (EPA 1985) was published on November 20, 1985, and a significantly revised version (EPA 1988a) was proposed December 21, 1988 in response to SARA. The proposed NCP is organized into the following subparts:

- Subpart A -- Introduction
- Subpart B -- Responsibility and Organization for Response
- Subpart C -- Planning and Preparedness
- Subpart D -- Operational Response Phases for Oil Removal
- Subpart E -- Hazardous Substance Response
- Subpart F -- State Involvement in Hazardous Substance Response
- Subpart G -- Trustees for Natural Resources
- Subpart H -- Participation by Other Persons
- Subpart I -- Administrative Record for Selection of Response Action
- Subpart J -- Use of Dispersants and Other Chemicals

Subpart E, Hazardous Substance Response, contains a detailed plan covering the entire range of authorized activities involved in abating and remedying releases or threats of releases of hazardous substances, pollutants, and contaminants. It contains provisions for both removal and remedial response. The remedial response process set forth by the proposed NCP is a seven-step process, as described below. Risk information plays a role in each step.

Site discovery or notification. Releases of hazardous substances, pollutants, or contaminants identified by federal, state, or local government agencies or private parties are reported to the National Response Center or EPA. Upon discovery, such potential sites are screened to identify release situations warranting further remedial response consideration. These sites are entered into the CERCLA Information System (CERCLIS). This computerized system serves as a data base of site information and tracks the change in status of a site through the response process. Risk information is used to determine which substances are hazardous and, in some cases, the quantities that constitute a release that must be reported (i.e., a reportable quantity, or RQ, under CERCLA section 103(a)).

Preliminary assessment and site inspection (PA/SI). The preliminary assessment involves

collection and review of all available information and may include offsite reconnaissance to evaluate the source and nature of hazardous substances present and to identify the responsible party(ies). At the conclusion of the preliminary assessment, a site may be referred for further action, or a determination may be made that no further action is needed. Site inspections, which follow the preliminary assessment for sites needing further action, routinely include the collection of samples and are conducted to help determine the extent of the problem and to obtain information needed to determine whether a removal action is warranted. If, based on the site inspection, it appears likely that the site should be considered for inclusion on the National Priorities List (NPL), a listing site inspection (LSI) is conducted. The LSI is a more extensive investigation than the SI, and a main objective of the LSI is to collect sufficient data about a site to support Hazard Ranking System (HRS) scoring. One of the main objectives of the PA/SI is to collect risk-related information for sites so that the site can be scored using the HRS and priorities may be set for more detailed studies, such as the RI/FS.

Establishing priorities for remedial action. Sites are scored using the HRS, based on data from the PA/SI/LSI. The HRS scoring process is the primary mechanism for determining the sites to be included on the NPL and, therefore, the sites eligible for Superfund-financed remedial action. The HRS is a numerical scoring model that is based on many of the factors affecting risk at a site. A revised version of the HRS (EPA 1988b) was proposed December 23, 1988.

Remedial investigation/feasibility study (RI/FS). As described in Section 1.1, the RI/FS is the framework for determining appropriate remedial actions at Superfund sites. Although RI/FS activities technically are removal actions and therefore not restricted to sites on the NPL (see sections 101(23) and 104(b) of CERCLA), they most frequently are undertaken at NPL sites. Remedial investigations are conducted to characterize the contamination at the site and to obtain information needed to identify, evaluate, and select cleanup alternatives. The feasibility study includes an analysis of alternatives based on the nine NCP evaluation criteria. The human health evaluation described in this manual, and the environmental evaluation described elsewhere, are the guidance for developing risk information in the RI/FS.

Selection of remedy. The primary consideration in selecting a remedy is that it be protective of human health and the environment, by eliminating, reducing, or controlling risks posed through each pathway. Thus, the risk information developed in the RI/FS is a key input to remedy selection. The results of the RI/FS are reviewed to identify a preferred alternative, which is announced to the public in a Proposed Plan. Next, the lead agency reviews any resulting public comments on the Proposed Plan, consults with the support agencies to evaluate whether the preferred alternative is still the most appropriate, and then makes a final decision. A record of decision (ROD) is written to document the rationale for the selected remedy.

Remedial design/remedial action. The detailed design of the selected remedial action is developed and then implemented. The risk information developed previously in the RI/FS helps refine the remediation goals that the remedy will attain.

Five-year review. Section 121(c) of CERCLA requires a periodic review of remedial actions, at least every five years after initiation of such action, for as long as hazardous substances, pollutants, or contaminants that may pose a threat to human health or the environment remain at the site. If it is determined during a five-year review that the action no longer protects human health and the environment, further remedial actions will need to be considered.

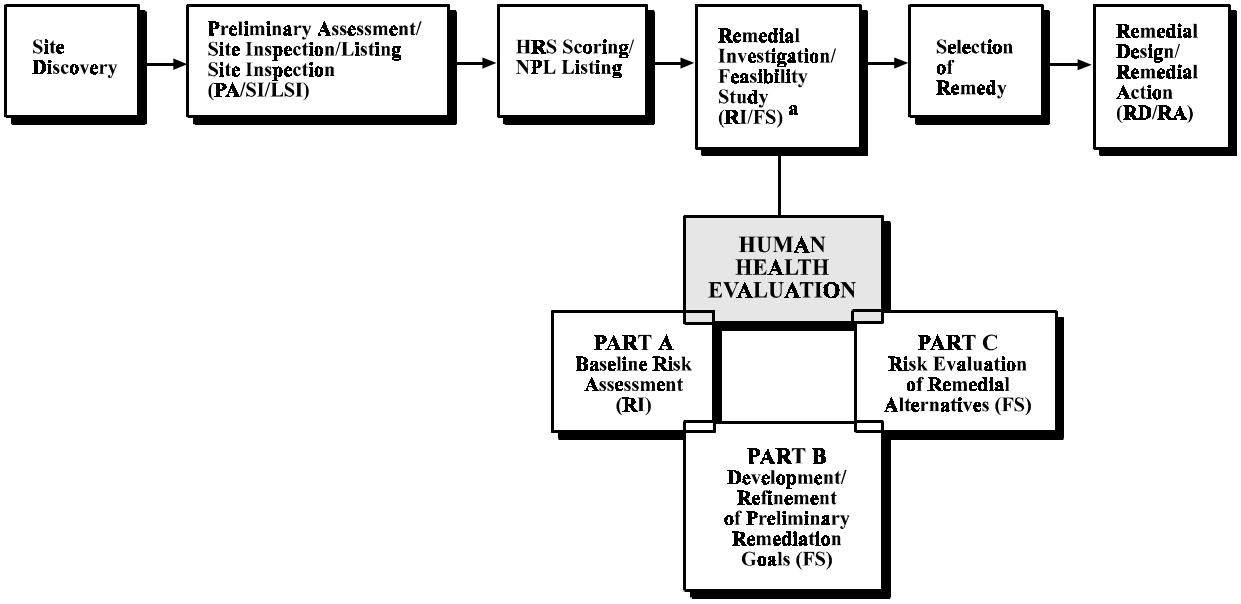
Exhibit 2-2 diagrams the general steps of the Superfund remedial process, indicating where in the process the various parts of the human health evaluation are conducted.

2.1.3 REMEDIAL INVESTIGATION/ FEASIBILITY STUDY GUIDANCE

EPA's interim final Guidance for Conducting Remedial Investigations and Feasibility Studies Under CERCLA (EPA 1988c) provides a detailed

EXHIBIT 2-2

ROLE OF THE HUMAN HEALTH EVALUATION IN THE SUPERFUND REMEDIAL PROCESS



[a] The RI/FS can be undertaken prior to NPL listing.

structure for conducting field studies to support remedial decisions and for identifying, evaluating, and selecting remedial action alternatives under CERCLA. This 1988 guidance document is a revision of two separate guidances for remedial investigations and for feasibility studies published in 1985. These guidances have been consolidated into a single document and revised to:

- reflect new emphasis and provisions of SARA;
- incorporate aspects of new or revised guidance related to RI/FSs;
- incorporate management initiatives designed to streamline the RI/FS process; and
- reflect experience gained from previous RI/FS projects.

The RI/FS consists of the following general steps:

- project scoping (during the RI);
- site characterization (RI);
- establishment of remedial action objectives (FS);
- development and screening of alternatives (FS); and
- detailed analysis of alternatives (FS).

Because Section 1.1 describes each of these steps, focusing on the role that risk information plays in the RI/FS, a discussion of the steps is not repeated here. The RI/FS guidance provides the context into which the human health evaluation fits and should be used in conjunction with this manual.

2.1.4 ARARS GUIDANCE

The interim final CERCLA *Compliance with Other Laws Manual* (EPA 1988d; EPA 1989a), or ARARs guidance, was developed to assist in the selection of onsite remedial actions that meet the applicable or relevant and appropriate requirements (ARARs) of the Resource Conservation and Recovery Act (RCRA), Clean Water Act (CWA), Safe Drinking Water Act (SDWA), Clean Air Act (CAA), and other federal and state environmental laws, as required by CERCLA section 121. Part I of the manual discusses the overall procedures for identifying ARARs and provides guidance on the interpretation and analysis of RCRA requirements. Specifically:

- Chapter 1 defines "applicable" and "relevant and appropriate," provides matrices listing potential chemical-specific, location-specific, and action-specific requirements from RCRA, CWA, and SDWA, and provides general procedures for identifying and analyzing requirements;
- Chapter 2 discusses special issues of interpretation and analysis involving RCRA requirements, and provides guidance on when RCRA requirements will be ARARs for CERCLA remedial actions;
- Chapter 3 provides guidance for compliance with CWA substantive (for onsite and offsite actions) and administrative (for offsite actions) requirements for direct discharges, indirect discharges, and dredge and fill activities;
- Chapter 4 provides guidance for compliance with requirements of the SDWA that may be applicable or relevant and appropriate to CERCLA sites; and
- Chapter 5 provides guidance on consistency with policies for ground-water protection.

The manual also contains a hypothetical scenario illustrating how ARARs are identified and used, and an appendix summarizing the provisions of RCRA, CWA, and SDWA.

Part II of the ARARs guidance covers the Clean Air Act, other federal statutes, and state requirements. Specifically:

- Chapter 1 provides an introduction to Part II of the guidance, and also includes extensive summary tables;

- Chapter 2 describes Clean Air Act requirements and related RCRA and state requirements;

- Chapters 3 and 4 provide guidance for compliance with several other federal statutes;

- Chapter 5 discusses potential ARARs for sites contaminated with radioactive substances;

- Chapter 6 addresses requirements specific to mining, milling, or smelting sites; and

- Chapter 7 provides guidance on identifying and complying with state ARARs.

2.1.5 SUPERFUND EXPOSURE ASSESSMENT MANUAL

The *Superfund Exposure Assessment Manual* (EPA 1988e), which was developed by the Superfund program specifically as a companion document to the original Superfund Public Health Evaluation Manual (EPA 1986), provides RPMs and regional risk assessors with the guidance necessary to conduct exposure assessments that meet the needs of the Superfund human health risk evaluation process. Specifically, the manual:

- provides an overall description of the integrated exposure assessment as it is applied to uncontrolled hazardous waste sites; and

- serves as a source of reference concerning the use of estimation procedures and computer modeling techniques for the analysis of uncontrolled sites.

The analytical process outlined in the *Superfund Exposure Assessment Manual* provides a framework for the assessment of exposure to contaminants at or migrating from uncontrolled hazardous waste sites. The application of both monitoring and modeling procedures to the exposure assessment process is outlined in the manual. This process considers all contaminant releases and exposure routes and assures that an adequate level of analytical detail is applied to support the human health risk assessment process.

The exposure assessment process described in the *Superfund Exposure Assessment Manual* is structured in five segments:

(1) analysis of contaminant releases from a subject site into environmental media;

(2) evaluation of the transport and environmental fate of the contaminants released;

(3) identification, enumeration, and characterization of potentially exposed populations;

(4) integrated exposure analysis; and

(5) uncertainty analysis.

Two recent publications from EPA's Office of Research and Development, the *Exposure Factors Handbook* (EPA 1989b) and the *Exposure Assessment Methods Handbook* (EPA 1989c), provide useful information to supplement the Superfund Exposure Assessment Manual. All three of these key exposure assessment references should be used in conjunction with Chapter 6 of this manual.

2.2 RELATED SUPERFUND STUDIES

This section identifies and briefly describes other Superfund studies related to, and sometimes confused with, the RI/FS human health evaluation. It contrasts the objectives and methods and clarifies the relationships of these other studies with RI/FS health risk assessments. The types of studies discussed are endangerment assessments, ATSDR health assessments, and ATSDR health studies.

2.2.1 ENDANGERMENT ASSESSMENTS

Before taking enforcement action against parties responsible for a hazardous waste site, EPA must determine that an imminent and substantial endangerment to public health or the environment

exists as a result of the site. Such a legal determination is called an endangerment assessment. For remedial sites, the process for analyzing whether there may be an endangerment is described in this Human Health Evaluation Manual and its companion Environmental Evaluation Manual. In the past, an endangerment assessment often was prepared as a study separate from the baseline risk assessment. With the passage of SARA and changes in Agency practice, the need to perform a detailed endangerment assessment as a separate effort from the baseline risk assessment has been eliminated.

For administrative orders requiring a remedial design or remedial action, endangerment assessment determinations are now based on information developed in the site baseline risk assessment. Elements included in the baseline risk assessment conducted at a Superfund site during the RI/FS process fully satisfy the informational requirements of the endangerment assessment. These elements include the following:

- identification of the hazardous wastes or hazardous substances present in environmental media;
- assessment of exposure, including a characterization of the environmental fate and transport mechanisms for the hazardous wastes and substances present, and of exposure pathways;
- assessment of the toxicity of the hazardous wastes or substances present;
- characterization of human health risks; and
- characterization of the impacts and/or risks to the environment.

The human health and environmental evaluations that are part of the RI/FS are conducted for purposes of determining the baseline risks posed by the site, and for ensuring that the selected remedy will be protective of human health and the environment. The endangerment assessment is used to support litigation by determining that an imminent and substantial endangerment exists. Information presented in the human health and environmental evaluations is basic to the legal determination of endangerment.

In 1985, EPA produced a draft manual specifically written for endangerment assessment, the Endangerment Assessment Handbook. EPA has determined that a guidance separate from the Risk Assessment Guidance for Superfund (Human Health Evaluation Manual and Environmental Evaluation Manual) is not required for endangerment assessment; therefore, the Endangerment Assessment Handbook will not be made final and should no longer be used.

2.2.2 ATSDR HEALTH ASSESSMENTS

CERCLA section 104(i), as amended, requires the Agency for Toxic Substances and Disease Registry (ATSDR) to conduct health assessments for all sites listed or proposed to be listed on the NPL. A health assessment includes a preliminary assessment of the potential threats that individual sites and facilities pose to human health. The health assessment is required to be completed "to the maximum extent practicable" before completion of the RI/FS. ATSDR personnel, state personnel (through cooperative agreements), or contractors follow six basic steps, which are based on the same general risk assessment framework as the EPA human health evaluation:

(1) evaluate information on the site's physical, geographical, historical, and operational setting, assess the demographics of nearby populations, and identify health concerns of the affected community(ies);

(2) determine contaminants of concern associated with the site;

(3) identify and evaluate environmental pathways;

(4) identify and evaluate human exposure pathways;

(5) identify and evaluate public health implications based on available medical and toxicological information; and

(6) develop conclusions concerning the health threat posed by the site and make recommendations regarding further public health activities.

The purpose of the ATSDR health assessment is to assist in the evaluation of data and information on the release of toxic substances into the environment in order to assess any current or future impact on public health, develop health advisories or other health-related recommendations, and identify studies or actions needed to evaluate and prevent human health effects. Health assessments are intended to help public health and regulatory officials determine if actions should be taken to reduce human exposure to hazardous substances and to recommend whether additional information on human exposure and associated risks is needed. Health assessments also are written for the benefit of the informed community associated with a site, which could include citizen groups, local leaders, and health professionals.

Several important differences exist between EPA human health evaluations and ATSDR health assessments. EPA human health evaluations include quantitative, substance-specific estimates of the risk that a site poses to human health. These estimates depend on statistical and biological models that use data from human epidemiologic investigations and animal toxicity studies. The information generated from a human health evaluation is used in risk management decisions to establish cleanup levels and select a remedial alternative.

ATSDR health assessments, although they may employ quantitative data, are more qualitative in nature. They focus not only on the possible health threats posed by chemical contaminants attributable to a site, but consider all health threats, both chemical and physical, to which residents near a site may be subjected. Health assessments focus on the medical and public health concerns associated with exposures at a site and discuss especially sensitive populations, toxic mechanisms, and possible disease outcomes. EPA considers the information in a health assessment along with the results of the baseline risk assessment to give a complete picture of health threats. Local health professionals and residents use the information to understand the potential health threats posed by specific waste sites. Health assessments may lead to pilot health effects studies, epidemiologic studies, or establishment of exposure or disease registries.

EPA's Guidance for Coordinating ATSDR Health Assessment Activities with the Superfund Remedial Process (EPA 1987) provides information to EPA and ATSDR managers for use in coordinating human health evaluation activities. (Section 2.1, in its discussion of CERCLA, provides further information on the statutory basis of ATSDR health assessments.)

2.2.3 ATSDR HEALTH STUDIES

After conducting a health assessment, ATSDR may determine that additional health effects information is needed at a site and, as a result, may undertake a pilot study, a full-scale epidemiological study, or a disease registry. Three types of pilot studies are predominant:

(1) a symptom/disease prevalence study consisting of a measurement of self-reported disease occurrence, which may be validated through medical records if they are available;

(2) a human exposure study consisting of biological sampling of persons who have a potentially high likelihood of exposure to determine if actual exposure can be verified; and

(3) a cluster investigation study consisting of an investigation of putative disease clusters to determine if the cases of a disease are excessively high in the concerned community.

A full-scale epidemiological study is an analytic investigation that evaluates the possible causal relationships between exposure to hazardous substances and disease outcome by testing a scientific hypothesis. Such an epidemiological study is usually not undertaken unless a pilot study reveals widespread exposure or increased prevalence of disease.

ATSDR, in cooperation with the states, also may choose to follow up the results of a health assessment by establishing and maintaining national

registries of persons exposed to hazardous substances and persons with serious diseases or illness. A registry is a system for collecting and maintaining, in a structured record, information on specific persons from a defined population. The purpose of a registry of persons exposed to hazardous substances is to facilitate development of new scientific knowledge through identification and subsequent follow-up of persons exposed to a defined substance at selected sites.

Besides identifying and tracking of exposed persons, a registry also is used to coordinate the clinical and research activities that involve the registrants. Registries serve an important role in assuring the uniformity and quality of the collected data and ensuring that data collection is not duplicative, thereby reducing the overall burden to exposed or potentially exposed persons.

REFERENCES FOR CHAPTER 2

Environmental Protection Agency (EPA). 1985. National Oil and Hazardous Substances Pollution Contingency Plan. Final Rule. 50 Federal Register 47912 (November 20, 1985).

Environmental Protection Agency (EPA). 1986. Superfund Public Health Evaluation Manual. Office of Emergency and Remedial Response. EPA/540/1-86/060. (OSWER Directive 9285.4-1).

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CHAPTER 3

GETTING STARTED: PLANNING FOR THE HUMAN HEALTH EVALUATION IN THE RI/FS

This chapter discusses issues related to planning the human health evaluation conducted during the RI/FS. It presents the goals of the RI/FS process as a whole and the human health evaluation in particular (Sections 3.1 and 3.2). It next discusses the way in which a site that is divided into operable units should be treated in the human health evaluation (Section 3.3). RI/FS scoping is discussed in Section 3.4, and Section 3.5 addresses the level of effort and detail necessary for a human health evaluation.

3.1 GOAL OF THE RI/FS

The goal of the RI/FS is to gather information sufficient to support an informed risk management decision regarding which remedy appears to be most appropriate for a given site. The RI/FS provides the context for all site characterization activity, including the human health evaluation. To attain this goal efficiently, EPA must identify and characterize hazards in a way that will contribute directly to the selection of an appropriate remedy. Program experience has shown that Superfund sites are complex, and are characterized by heterogeneous wastes, extreme variability in contamination levels, and a variety of environmental settings and potential exposure pathways. Consequently, complete characterization of a site during the RI/FS, in the sense of eliminating uncertainty, is not feasible, cost-effective, or necessary for selection of appropriate remedies. This view has motivated the "streamlined approach" EPA is taking to help accomplish the goal of completing an RI/FS in 18 months at a cost of $750,000 per operable unit and $1.1 million per site. The streamlined approach recognizes that the elimination of all uncertainties is not possible or necessary and instead strives only for sufficient data to generally characterize a site and support remedy selection. The resulting remedies are flexible and incorporate specific contingencies to respond to new information discovered during remedial action and follow-up.

3.2 GOAL OF THE RI/FS HUMAN HEALTH EVALUATION

As part of the effort to streamline the process and reduce the cost and time required to conduct the RI/FS, the Superfund human health evaluation needs to focus on providing information necessary to justify action at a site and to select the best remedy for the site. This should include characterizing the contaminants, the potential exposures, and the potentially exposed population sufficiently to determine what risks need to be reduced or eliminated and what exposures need to be prevented. It is important to recognize that information should be developed only to help EPA determine what actions are necessary to reduce risks, and not to fully characterize site risks or eliminate all uncertainty from the analysis.

In a logical extension of this view, EPA has made a policy decision to use, wherever appropriate, standardized assumptions, equations, and values in the human health evaluation to achieve the goal of streamlined assessment. This approach has the added benefit of making human health evaluation easier to review, easier to understand, and more consistent from site to site. Developing unique exposure assumptions or non-standard methods of

risk assessment should not be necessary for most sites. Where justified by site-specific data or by changes in knowledge over time, however, non-standard methods and assumptions may be used.

3.3 OPERABLE UNITS

Current practice in designing remedies for Superfund sites often divides sites into operable units that address discrete aspects of the site (e.g., source control, ground-water remediation) or different geographic portions of the site. The NCP defines operable unit as "a discrete action that comprises an incremental step toward comprehensively addressing site problems." RI/FSs may be conducted for the entire site and operable units broken out during or after the feasibility study, or operable units may be treated individually from the start, with focused RI/FSs conducted for each operable unit. The best way to address the risks of the operable unit will depend on the needs of the site.

The human health evaluation should focus on the subject of the RI/FS, whether that is an operable unit or the site as a whole. The baseline risk assessment and other risk information gathered will provide the justification for taking the action for the operable unit. At the same time, personnel involved in conducting the human health evaluation for a focused RI/FS must be mindful of other potential exposure pathways, and other actions that are being contemplated for the site to address other potential exposures. Risk analysts should foresee that exposure pathways outside the scope of the focused RI/FS may ultimately be combined with exposure pathways that are directly addressed by the focused RI/FS. Considering risks from all related operable units should prevent the unexpected discovery of high multiple pathway risks during the human health evaluation for the last operable unit. Consider, for example, a site that will be addressed in two operable units: a surface soil cleanup at the contamination source and a separate ground-water cleanup. Risks associated with residuals from the soil cleanup and the ground-water cleanup may need to be considered as a cumulative total if there is the potential for exposure to both media at the same time.

3.4 RI/FS SCOPING

Planning the human health evaluation prior to beginning the detailed analysis is an essential step in the process. The RPM must make up-front decisions about, for example, the scope of the baseline risk assessment, the appropriate level of detail and documentation, trade-offs between depth and breadth in the analysis, and the staff and monetary resources to commit.

Scoping is the initial planning phase of the RI/FS process, and many of the planning steps begun here are continued and refined in later phases. Scoping activities typically begin with the collection of existing site data, including data from previous investigations such as the preliminary assessment and site inspection. On the basis of this information, site management planning is undertaken to identify probable boundaries of the study area, to identify likely remedial action objectives and whether interim actions may be necessary or appropriate, and to establish whether the site may best be remedied as one site or as several separate operable units. Once an overall management strategy is agreed upon, the RI/FS for a specific project or the site as a whole is planned.

The development of remedial alternatives usually begins during or soon after scoping, when likely response scenarios may first be identified. The development of alternatives requires:

- identifying remedial action objectives;
- identifying potential treatment, resource recovery, and containment technologies that will satisfy these objectives; and
- screening the technologies based on their effectiveness, implementability, and cost.

Remedial alternatives may be developed to address a contaminated medium, a specific area of the site, or the entire site. Alternative remedial actions for specific media and site areas either can be carried through the FS process separately or combined into comprehensive alternatives for the entire site. The approach is flexible to allow alternatives to be considered in combination at various points in the process. The RI/FS guidance discusses planning in greater detail.

3.5 LEVEL OF EFFORT/LEVEL OF DETAIL OF THE HUMAN HEALTH EVALUATION

An important part of scoping is determining the appropriate level of effort/level of detail necessary for the human health evaluation. Human health evaluation can be thought of as spanning a continuum of complexity, detail, and level of effort, just as sites vary in conditions and complexity. Some of the site-specific factors affecting level of effort that the RPM must consider include the following:

- number and identity of chemicals present;
- availability of ARARs and/or applicable toxicity data;
- number and complexity of exposure pathways (including complexity of release sources and transport media), and the need for environmental fate and transport modeling to supplement monitoring data;
- necessity for precision of the results, which in turn depends on site conditions such as the extent of contaminant migration, characteristics of potentially exposed populations, and enforcement considerations (additional quantification may be warranted for some enforcement sites); and
- quality and quantity of available monitoring data.[1]

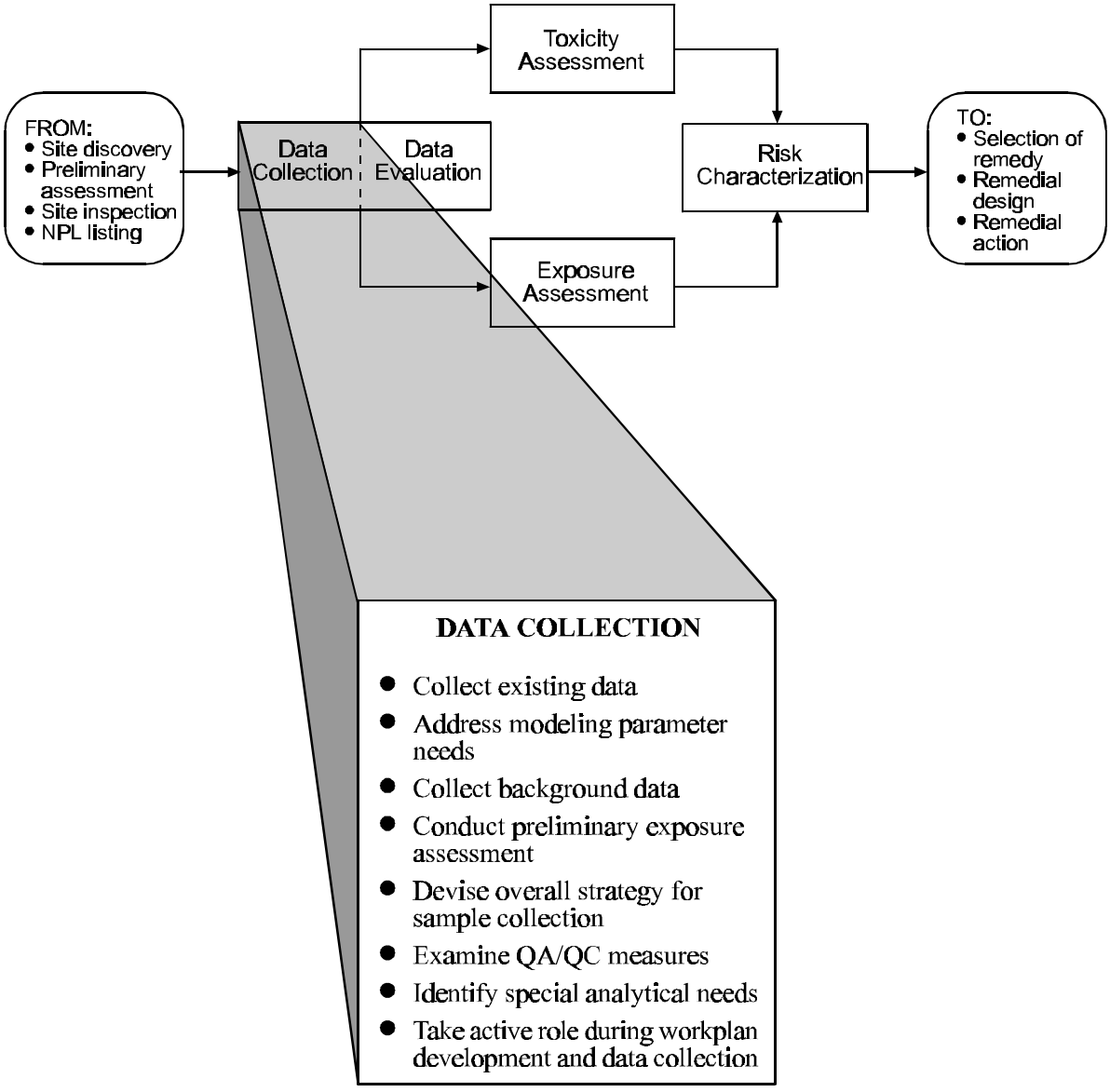
This manual is written to address the most complex sites, and as a result not all of the steps and procedures of the Superfund human health evaluation process described in this manual apply to all remedial sites. For example, Section 6.6 provides procedures and equations for estimating chemical intakes through numerous exposure routes, although for many sites, much of this information will not apply (e.g., the exposure route does not exist or is determined to be relatively unimportant). This manual establishes a generic framework that is broadly applicable across sites, and it provides specific procedures that cover a range of sites or situations that may or may not be appropriate for any individual site. As a consequence of attempting to cover the wide variety of Superfund site conditions, some of the process components, steps, and techniques described in the manual do not apply to some sites. In addition, most of the components can vary greatly in level of detail. Obviously, determining which elements of the process are necessary, which are desirable, and which are extraneous is a key decision for each site. All components should not be forced into the assessment of a site, and the evaluation should be limited to the complexity and level of detail necessary to adequately assess risks for the purposes described in Sections 3.1 and 3.2.

Planning related to the collection and analysis of chemical data is perhaps the most important planning step. Early coordination among the risk assessors, the remainder of the RI/FS team, representatives of other agencies involved in the risk assessment or related studies (e.g., ATSDR, natural resource trustees such as the Department of the Interior, state agencies), and the RPM is essential and preferably should occur during the scoping stage of the RI/FS. Detailed guidance on planning related to collection and analysis of chemical data is given in Chapter 4 of this manual.

ENDNOTE FOR CHAPTER 3

1. All site monitoring data must be subjected to appropriate quality assurance/quality control programs. Lack of acceptable data may limit by necessity the amount of data available for the human health evaluation, and therefore may limit the scope of the evaluation. Acceptability is determined by whether data meet the appropriate data quality objectives (see Section 4.1.2).

CHAPTER 4
DATA COLLECTION



CHAPTER 4

DATA COLLECTION

This chapter discusses procedures for acquiring reliable chemical release and exposure data for quantitative human health risk assessment at hazardous waste sites.[1] The chapter is intended to be a limited discussion of important sampling considerations with respect to risk assessment; it is not intended to be a complete guide on how to collect data or design sampling plans.

Following a general background section (Section 4.1), this chapter addresses the following eight important areas:

(1) review of available site information (Section 4.2);

(2) consideration of modeling parameter needs (Section 4.3);

(3) definition of background sampling needs (Section 4.4);

(4) preliminary identification of potential human exposure (Section 4.5);

(5) development of an overall strategy for sample collection (Section 4.6);

(6) definition of required QA/QC measures (Section 4.7);

(7) evaluation of the need for Special Analytical Services (Section 4.8); and

(8) activities during workplan development and data collection (Section 4.9).

4.1 BACKGROUND INFORMATION USEFUL FOR DATA COLLECTION

This section provides background information on the types of data needed for risk assessment, overall data needs of the RI/FS, reasons and steps for identifying risk assessment data needs early, use of the *Data Quality Objectives for Remedial Response Activities* (EPA 1987a,b, hereafter referred to as the DQO guidance), and other data concerns.

4.1.1 TYPES OF DATA

In general, the types of site data needed for a baseline risk assessment include the following:

- contaminant identities;

ACRONYMS FOR CHAPTER 4

CLP = Contract Laboratory Program
DQO = Data Quality Objectives
FIT = Field Investigation Team
FSP = Field Sampling Plan
HRS = Hazard Ranking System
IDL = Instrument Detection Limit
MDL = Method Detection Limit
PA/SI = Preliminary Assessment/Site Inspection
QA/QC = Quality Assurance/Quality Control
QAPjP = Quality Assurance Project Plan
RAS = Routine Analytical Services
RI/FS = Remedial Investigation/Feasibility Study
SAP = Sampling and Analysis Plan
SAS = Special Analytical Services
SMO = Sample Management Office
SOW = Statement of Work
TAL = Target Analyte List
TCL = Target Compound List
TIC = Tentatively Identified Compound

DEFINITIONS FOR CHAPTER 4

Analytes. The chemicals for which a sample is analyzed.

Anthropogenic Background Levels. Concentrations of chemicals that are present in the environment due to human-made, non-site sources (e.g., industry, automobiles).

Contract Laboratory Program (CLP). Analytical program developed for Superfund waste site samples to fill the need for legally defensible analytical results supported by a high level of quality assurance and documentation.

Data Quality Objectives (DQOs). Qualitative and quantitative statements to ensure that data of known and documented quality are obtained during an RI/FS to support an Agency decision.

Field Sampling Plan (FSP). Provides guidance for all field work by defining in detail the sampling and data gathering methods to be used on a project.

Naturally Occurring Background Levels. Ambient concentrations of chemicals that are present in the environment and have not been influenced by humans (e.g., aluminum, manganese).

Quality Assurance Project Plan (QAPjP). Describes the policy, organization, functional activities, and quality assurance and quality control protocols necessary to achieve DQOs dictated by the intended use of the data (*RI/FS Guidance*).

Routine Analytical Services (RAS). The set of CLP analytical protocols that are used to analyze most Superfund site samples. These protocols are provided in the EPA Statements of Work for the CLP (*SOW for Inorganics*, *SOW for Organics*) and must be followed by every CLP laboratory.

Sampling and Analysis Plan (SAP). Consists of a Quality Assurance Project Plan (QAPjP) and a Field Sampling Plan (FSP).

Sample Management Office (SMO). EPA contractor providing management, operational, and administrative support to the CLP to facilitate optimal use of the program.

Special Analytical Services (SAS). Non-standardized analyses conducted under the CLP to meet user requirements that cannot be met using RAS, such as shorter analytical turnaround time, lower detection limits, and analysis of non-standard matrices or non-TCL compounds.

Statement of Work (SOW) for the CLP. A document that specifies the instrumentation, sample handling procedures, analytical parameters and procedures, required quantitation limits, quality control requirements, and report format to be used by CLP laboratories. The SOW also contains the TAL and TCL.

Target Analyte List (TAL). Developed by EPA for Superfund site sample analyses. The TAL is a list of 23 metals plus total cyanide routinely analyzed using RAS.

Target Compound List (TCL). Developed by EPA for Superfund site sample analyses. The TCL is a list of analytes (34 volatile organic chemicals, 65 semivolatile organic chemicals, 19 pesticides, 7 polychlorinated biphenyls, 23 metals, and total cyanide) routinely analyzed using RAS.

- contaminant concentrations in the key sources and media of interest;[2]
- characteristics of sources, especially information related to release potential; and
- characteristics of the environmental setting that may affect the fate, transport, and persistence of the contaminants.

Most of these data are obtained during the course of a remedial investigation/feasibility study (RI/FS). Other sources of information, such as preliminary assessment/site inspection (PA/SI) reports, also may be available.

4.1.2 DATA NEEDS AND THE RI/FS

The RI/FS has four primary data collection components:

(1) characterization of site conditions;
(2) determination of the nature of the wastes;
(3) risk assessment; and
(4) treatability testing.

The site and waste characterization components of the RI/FS are intended to determine characteristics of the site (e.g., ground-water movement, surface water and soil characteristics) and the nature and extent of contamination through sampling and analysis of sources and potentially contaminated media. Quantitative risk assessment, like site characterization, requires data on concentrations of contaminants in each of the source areas and media of concern. Risk assessment also requires information on other variables necessary for evaluating the fate, transport, and persistence of contaminants and estimating current and potential human exposure to these contaminants. Additional data might be required for environmental risk assessments (see EPA 1989a).

Data also are collected during the RI/FS to support the design of remedial alternatives. As discussed in the DQO guidance (EPA 1987a,b), such data include results of analyses of contaminated media "before and after" bench-scale treatability tests. This information usually is not appropriate for use in a baseline risk assessment because these media typically are assessed only for a few individual parameters potentially affected by the treatment being tested. Also, initial treatability testing may involve only a screening analysis that generally is not sensitive enough and does not have sufficient quality assurance/quality control (QA/QC) procedures for use in quantitative risk assessment.

4.1.3 EARLY IDENTIFICATION OF DATA NEEDS

Because the RI/FS and other site studies serve a number of different purposes (e.g., site and waste characterization, design of remedial alternatives), only a subset of this information generally is useful for risk assessment. To ensure that all risk assessment data needs will be met, it is important to identify those needs early in the RI/FS planning for a site. The earlier the requirements are identified, the better the chances are of developing an RI/FS that meets the risk assessment data collection needs.

One of the earliest stages of the RI/FS at which risk assessment data needs can be addressed is the site scoping meeting. As discussed in the *Guidance for Conducting Remedial Investigations and Feasibility Studies Under CERCLA* (EPA 1988a, hereafter referred to as RI/FS guidance), the scoping meeting is part of the initial planning phase of site remediation. It is at this meeting that the data needs of each of the RI/FS components (e.g., site and waste characterization) are addressed together. Scoping meeting attendees include the RPM, contractors conducting the RI/FS (including the baseline risk assessment), onsite personnel (e.g., for construction), and natural resource trustees (e.g., Department of Interior). The scoping meeting allows development of a comprehensive sampling and analysis plan (SAP) that will satisfy the needs of each RI/FS component while helping to ensure that time and budget constraints are met. Thus, in addition to aiding the effort to meet the risk assessment data needs, this meeting can help integrate these needs with other objectives of the RI/FS and thereby help make maximum use of available resources and avoid duplication of effort.

During scoping activities, the risk assessor should identify, at least in preliminary fashion, the type and duration of possible exposures (e.g., chronic, intermittent), potential exposure routes (e.g., ingestion of fish, ingestion of drinking water, inhalation of dust), and key exposure points (e.g., municipal wells, recreation areas) for each medium. The relative importance of the potential exposure routes and exposure points in determining risks should be discussed, as should the consequences of not studying them adequately. Section 4.5 and Chapter 6 provide guidance for identifying exposure pathways that may exist at hazardous waste sites. If potential exposure pathways are identified early in the RI/FS process, it will be easier to reach a decision on the number, type, and location of samples needed to assess exposure.

During the planning stages of the RI/FS, the risk assessor also should determine if non-routine (i.e., lower) quantitation limits are needed to adequately characterize risks at a site. Special Analytical Services (SAS) of the EPA Contract Laboratory Program (CLP) may be needed to achieve such lower quantitation limits. (See Section 4.8 for additional information concerning quantitation limits.)

4.1.4 USE OF THE DATA QUALITY OBJECTIVES (DQO) GUIDANCE

The DQO guidance (EPA 1987a,b) provides information on the review of site data and the determination of data quality needs for sampling (see the box below).

OVERVIEW OF DQO GUIDANCE

According to the DQO guidance (EPA 1987a and b), DQO are qualitative and quantitative statements established prior to data collection, which specify the quality of the data required to support Agency decisions during remedial response activities. The DQO for a particular site vary according to the end use of the data (i.e., whether the data are collected to support preliminary assessments/site inspections, remedial investigations/feasibility studies, remedial designs, or remedial actions).

The DQO process consists of three stages. In Stage 1 (Identify Decision Types), all available site information is compiled and analyzed in order to develop a conceptual model of the site that describes suspected sources, contaminant pathways, and potential receptors. The outcome of Stage 1 is a definition of the objectives of the site investigation and an identification of data gaps. Stage 2 (Identify Data Uses/Needs) involves specifying the data necessary to meet the objectives set in Stage 1, selecting the sampling approaches and the analytical options for the site, and evaluating multiple-option approaches to allow more timely or cost-effective data collection and evaluation. In Stage 3 (Design Data Collection Program), the methods to be used to obtain data of acceptable quality are specified in such products as the SAP or the workplan.

Use of this guidance will help ensure that all environmental data collected in support of RI/FS activities are of known and documented quality.

4.1.5 OTHER DATA CONCERNS

The simple existence of a data collection plan does not guarantee usable data. The risk assessor should plan an active role in oversight of data collection to ensure that relevant data have been obtained. (See Section 4.9 for more information on the active role that the risk assessor must play.)

After data have been collected, they should be carefully reviewed to identify reliable, accurate, and verifiable numbers that can be used to quantify risks. All analytical data must be evaluated to identify the chemicals of potential concern (i.e., those to be carried through the risk assessment). Chapter 5 discusses the criteria to be considered in selecting the subset of chemical data appropriate for baseline risk assessment. Data that do not meet the criteria are not included in the quantitative risk assessment; they can be discussed qualitatively in the risk assessment report, however, or may be the basis for further investigation.

4.2 REVIEW OF AVAILABLE SITE INFORMATION

Available site information must be reviewed to (1) determine basic site characteristics, (2) initially identify potential exposure pathways and exposure points, and (3) help determine data needs (including modeling needs). All available site information (i.e., information existing at the start of the RI/FS) should be reviewed in accordance with Stage 1 of the DQO process. Sources of available site information include:

- RI/FS scoping information;
- PA/SI data and Hazard Ranking System (HRS) documentation;
- listing site inspection (LSI) data (formally referred to as expanded site inspection, or ESI);
- photographs (e.g., EPA's Environmental Photographic Interpretation Center [EPIC]);
- records on removal actions taken at the site; and
- information on amounts of hazardous substances disposed (e.g., from site records).

If available, LSI (or ESI) data are especially useful because they represent fairly extensive site studies.

Based on a review of the existing data, the risk assessor should formulate a conceptual model of the site that identifies all potential or suspected sources of contamination, types and concentrations of contaminants detected at the site, potentially contaminated media, and potential exposure pathways, including receptors (see Exhibit 4-1). As

discussed previously, identification of potential exposure pathways, especially the exposure points, is a key element in the determination of data needs for the risk assessment. Details concerning development of a conceptual model for a site are provided in the DQO guidance (EPA 1987a,b) and the RI/FS guidance (EPA 1988a).

In most cases, site information available at the start of the RI/FS is insufficient to fully characterize the site and the potential exposure pathways. The conceptual model developed at this stage should be adequate to determine the remaining data needs. The remainder of this chapter addresses risk assessment data needs in detail.

4.3 ADDRESSING MODELING PARAMETER NEEDS

As discussed in detail in Chapter 6, contaminant release, transport, and fate models are often needed to supplement monitoring data when estimating exposure concentrations. Therefore, a preliminary site modeling strategy should be developed during RI/FS scoping to allow model input data requirements to be incorporated into the data collection requirements. This preliminary identification of models and other related data requirements will ensure that data for model calibration and validation are collected along with other physical and chemical data at the site. Exhibit 4-2 lists (by medium) several site-specific parameters often needed to incorporate fate and transport models in risk assessments.

Although default values for some modeling parameters are available, it is preferable to obtain site-specific values for as many input parameters as is feasible. If the model is not sensitive to a particular parameter for which a default value is available, then a default value may be used. Similarly, default values may be used if obtaining the site-specific model parameter would be too time consuming or expensive. For example, certain airborne dust emission models use a default value for the average wind speed at the site; this is done because representative measurements of wind speed at the site would involve significant amounts of time (i.e., samples would have to be collected over a large part of the year).

Some model parameters are needed only if the sampling conducted at a site is sufficient to support complex models. Such model parameters may not be necessary if only simple fate and transport models are used in the risk assessment.

4.4 DEFINING BACKGROUND SAMPLING NEEDS

Background sampling is conducted to distinguish site-related contamination from naturally occurring or other non-site-related levels of chemicals. The following subsections define the types of background contamination and provide guidance on the appropriate location and number of background samples.

4.4.1 TYPES OF BACKGROUND

There are two different types of background levels of chemicals:

(1) naturally occurring levels, which are ambient concentrations of chemicals present in the environment that have not been influenced by humans (e.g., aluminum, manganese); and

(2) anthropogenic levels, which are concentrations of chemicals that are present in the environment due to human-made, non-site sources (e.g., industry, automobiles).

Background can range from localized to ubiquitous. For example, pesticides -- most of which are not naturally occurring (anthropogenic) -- may be ubiquitous in certain areas (e.g., agricultural areas); salt runoff from roads during periods of snow may contribute high ubiquitous levels of sodium. Polycyclic aromatic hydrocarbons (PAHs) and lead are other examples of anthropogenic, ubiquitous chemicals, although these chemicals also may be present at naturally occurring levels in the environment due to natural sources (e.g., forest fires may be a source of PAHs, and lead is a natural component of soils in some areas).

EXHIBIT 4-1
ELEMENTS OF A CONCEPTUAL EVALUATION MODEL

	VARIABLES	HYPOTHESES TO BE TESTED
SOURCES	• CONTAMINANTS • CONCENTRATIONS • TIME • LOCATIONS	• SOURCE EXISTS • SOURCE CAN BE CONTAINED • SOURCE CAN BE REMOVED AND DISPOSED • SOURCE CAN BE TREATED
PATHWAYS	• MEDIA • RATES OF MIGRATION • TIME • LOSS AND GAIN FUNCTIONS	• PATHWAY EXISTS • PATHWAY CAN BE INTERRUPTED • PATHWAY CAN BE ELIMINATED
RECEPTORS	• TYPES • SENSITIVITIES • TIME • CONCENTRATIONS • NUMBERS	• RECEPTOR IS NOT IMPACTED BY MIGRATION OF CONTAMINANTS • RECEPTOR CAN BE RELOCATED • INSTITUTIONAL CONTROLS CAN BE APPLIED • RECEPTOR CAN BE PROTECTED

EXHIBIT 4-2

EXAMPLES OF MODELING PARAMETERS FOR WHICH INFORMATION MAY NEED TO BE OBTAINED DURING A SITE SAMPLING INVESTIGATION

Type of Modeling	Modeling Parameters[a]
Source Characteristics	Geometry, physical/chemical conditions, emission rate, emission strength, geography
Soil	Particle size, dry weight, pH, redox potential, mineral class, organic carbon and clay content, bulk density, soil porosity
Ground-water	Head measurements, hydraulic conductivity (pump and slug test results), saturated thickness of aquifer, hydraulic gradient, pH, redox potential, soil-water partitioning
Air	Prevailing wind direction, wind speeds, stability class, topography, depth of waste, contaminant concentration in soil and soil gas, fraction organic content of soils, silt content of soils, percent vegetation, bulk density of soil, soil porosity
Surface Water	Hardness, pH, redox potential, dissolved oxygen, salinity, temperature, conductivity, total suspended solids, flow rates, and depths for rivers/streams, estuary and embayment parameters such as tidal cycle, saltwater incursion extent, depth and area, lake parameters such as area, volume, depth, depth to thermocline
Sediment	Particle size distribution, organic content, pH, benthic oxygen conditions, water content
Biota	Dry weight, whole body, specific organ, and/or edible portion chemical concentrations, percent moisture, lipid content, size/age, life history stage

[a] These parameters are not necessarily limited to the type of modeling with which they are associated in this exhibit. For example, many of the parameters listed for surface water are also appropriate for sediments.

4.4.2 BACKGROUND SAMPLING LOCATIONS

Background samples are collected at or near the hazardous waste site in areas not influenced by site contamination. They are collected from each medium of concern in these offsite areas. That is, the locations of background samples must be areas that could not have received contamination from the site, but that do have the same basic characteristics as the medium of concern at the site.

Identifying background location requires knowing which direction is upgradient/upwind/upstream. In general, the direction of water flow tends to be relatively constant, whereas the direction of air flow is constantly changing. Therefore, the determination of background locations for air monitoring requires constant and concurrent monitoring of factors such as wind direction.

4.4.3 BACKGROUND SAMPLE SIZE

In appropriate circumstances, statistics may be used to evaluate background sample data. Because the number of background samples collected is important for statistical hypothesis testing, at some sites a statistician should be consulted when determining background sample size. At all sites, the RPM should decide the level of statistical analysis applicable to a particular situation.

Often, rigorous statistical analyses are unnecessary because site- and non-site-related contamination clearly differ. For most sites, the issue will not be whether a difference in chemical concentrations can be demonstrated between contaminated and background areas, but rather that of establishing a reliable representation of the extent (in three dimensions) of a contaminated area. However, statistical analyses are required at some sites, making a basic understanding of statistics necessary. The following discussion outlines some basic statistical concepts in the context of background data evaluation for risk assessment. (A general statistics textbook should be reviewed for additional detail. Also, the box below lists EPA guidance that might be useful.)

STATISTICAL METHODS GUIDANCE

Statistical Methods for Evaluating Groundwater Monitoring Data from Hazardous Waste Facilities (EPA 1988b)

Surface Impoundment Clean Closure Guidance Manual (EPA 1988c)

Love Canal Emergency Declaration Area Habitability Study (EPA 1988d)

Soils Sampling Quality Assurance Guide (EPA 1989b)

A statistical test of a hypothesis is a rule used for deciding whether or not a statement (i.e., the null hypothesis) should be rejected in favor of a specified alternative statement (i.e., the alternative hypothesis). In the context of background contamination at hazardous waste sites, the null hypothesis can be expressed as "there is no difference between contaminant concentrations in background areas and onsite," and the alternative hypothesis can be expressed as "concentrations are higher onsite." This expression of the alternative hypothesis implies a one-tailed test of significance.

The number of background samples collected at a site should be sufficient to accept or reject the null hypothesis with a specified likelihood of error. In statistical hypothesis testing there are two types of error. The null hypothesis may be rejected when it is true (i.e., a Type I error), or not rejected when it is false (i.e., a Type II error). An example of a Type I error at a hazardous waste site would be to conclude that contaminant concentrations in onsite soil are higher than background soil concentrations when in fact they are not. The corresponding Type II error would be to conclude that onsite contaminant concentrations are not higher than background concentrations when in fact they are. A Type I error could result in unnecessary remediation, while a Type II error could result in a failure to clean up a site when such an action is necessary.

In customary notations, α (alpha) denotes the probability that a Type I error will occur, and β (beta) denotes the probability that a Type II error will occur. Most statistical comparisons refer to α, also known as the level of significance of the test. If $\alpha = 0.05$, there is a 5 percent (i.e., 1 in 20) chance that we will conclude that concentrations of contaminants are higher than background when they actually are not.

Equally critical considerations in determining the number of background samples are β and a concept called "power." The power of a statistical test has the value $1 - \beta$ and is defined as the likelihood that the test procedure detects a false null hypothesis. Power functions for commonly used statistical tests can be found in most general statistical textbooks. Power curves are a function of α (which normally is fixed at 0.05), sample size (i.e., the number of background and/or onsite samples), and the amount of variability in the data. Thus, if a 15 percent likelihood of failing to detect a false null hypothesis is desired (i.e., $\beta = 0.15$), enough background samples must be collected to ensure that the power of the test is at least 0.85.

A small number of background samples increases the likelihood of a Type II error. If an insufficient number of background samples is collected, fairly large differences between site and background concentrations may not be statistically significant, even though concentrations in the many site samples are higher than the few background samples. To guard against this situation, the statistical power associated with the comparison of background samples with site samples should be evaluated.

In general, when trying to detect small differences as statistically significant, the number of background samples should be similar to the number of onsite samples that will be used for the comparison(s) (e.g., the number of samples taken from one well). (Note that this does not mean that the background sample size must equal the total number of onsite samples.) Due to the inherent variability of air concentrations (see Section 4.6), background sample size for air needs to be relatively large.

4.4.4 COMPARING BACKGROUND SAMPLES TO SITE-RELATED CONTAMINATION

The medium sampled influences the kind of statistical comparisons that can be made with background data. For example, air monitoring stations and ground-water wells are normally positioned based on onsite factors and gradient considerations. Because of this purposive placement (see Section 4.6.1), several wells or monitors cannot be assumed to be a random sample from a single population and hence cannot be evaluated collectively (i.e., the sampling results cannot be combined). Therefore, the information from each well or air monitor should be compared individually with background.

Because there typically are many site-related, media-specific sampling location data to compare with background, there usually is a "multiple comparison problem" that must be addressed. In general, the probability of experiencing a Type I error in the entire set of statistical tests increases with the number of comparisons being made. If $\alpha = 0.05$, there is a 1 in 20 chance of a Type I error in any single test. If 20 comparisons are being made, it therefore is likely that at least one Type I error will occur among all 20 tests. *Statistical Analysis of Ground-water Monitoring Data at RCRA Facilities* (EPA 1989c) is useful for designing sampling plans for comparing information from many fixed locations with background.

It may be useful at times to look at comparisons other than onsite versus background. For example, upgradient wells can be compared with downgradient wells. Also, there may be several areas within the site that should be compared for differences in site-related contaminant concentration. These areas of concern should be established before sampling takes place. If a more complicated comparison scheme is planned, a statistician should be consulted frequently to help distribute the sampling effort and design the analysis.

A statistically significant difference between background samples and site-related contamination should not, by itself, trigger a cleanup action. The remainder of this manual still must be applied so that the toxicological -- rather than simply the statistical -- significance of the contamination can be ascertained.

4.5 PRELIMINARY IDENTIFICATION OF POTENTIAL HUMAN EXPOSURE

A preliminary identification of potential human exposure provides much needed information for the SAP. This activity involves the identification of (1) media of concern, (2) areas of concern (i.e., general locations of the media to be sampled),[3] (3) types of chemicals expected at the site, and (4) potential routes of contaminant transport through the environment (e.g., inter-media transfer, food chain). This section provides general information on the preliminary identification of potential human exposure pathways, as well as specific information on the various media. (Also, see Chapter 6 for a detailed discussion of exposure assessment.)

4.5.1 GENERAL INFORMATION

Prior to discussing various specific exposure media, general information on the following is provided: media, types of chemicals, areas of concern, and routes of contaminant transport is addressed.

Media of concern (including biota). For risk assessment purposes, media of concern at a site are:

- any currently contaminated media to which individuals may be exposed or through which chemicals may be transported to potential receptors; and
- any currently uncontaminated media that may become contaminated in the future due to contaminant transport.

Several medium-specific factors in sampling may influence the risk assessment. For example, limitations in sampling the medium may limit the detailed evaluation of exposure pathways described in Chapter 6. To illustrate this, if soil samples are not collected at the surface of a site, then it may not be possible to accurately evaluate potential exposures involving direct contact with soils or exposures involving the release of contaminants from soils via wind erosion (with subsequent inhalation of airborne contaminants by exposed individuals). Therefore, based on the conceptual model of the site discussed previously, the risk assessor should make sure that appropriate samples are collected from each medium of concern.

Areas of concern. Areas of concern refer to the general sampling locations at or near the site. For large sites, areas of concern may be treated in the RI/FS as "operable units," and may include several media. Areas of concern also can be thought of as the locations of potentially exposed populations (e.g., nearest residents) or biota (e.g., wildlife feeding areas).

Areas of concern should be identified based on site-specific characteristics. These areas are chosen purposively by the investigators during the initial scoping meeting. Areas of concern should include areas of the site that:

(1) have different chemical types;

(2) have different anticipated concentrations or hot spots;

(3) are a release source of concern;

(4) differ from each other in terms of the anticipated spatial or temporal variability of contamination;

(5) must be sampled using different equipment; and/or

(6) are more or less costly to sample.

In some instances, the risk assessor may want to estimate concentrations that are representative of the site as a whole, in addition to each area of concern. In these cases, two conditions generally should be met in defining areas of concern: (1) the boundaries of the areas of concern should not

overlap and (2) all of the areas of concern together should account for the entire area of the site.

Depending on the exposure pathways that are being evaluated in the risk assessment, it may not be necessary to determine site-wide representative values. In this case, areas of concern do not have to account for the entire area of the site.

Types of chemicals. The types of chemicals expected at a hazardous waste site may dictate the site areas and media sampled. For example, certain chemicals (e.g., dioxins) that bioconcentrate in aquatic life also are likely to be present in the sediments. If such chemicals are expected at a particular site and humans are expected to ingest aquatic life, sampling of sediments and aquatic life for the chemicals may be particularly important.

Due to differences in the relative toxicities of different species of the same chemical (e.g., Cr^{+3} versus Cr^{+6}), the species should be noted when possible.

Routes of contaminant transport. In addition to medium-specific concerns, there may be several potential current and future routes of contaminant transport within a medium and between media at a site. For instance, discharge of ground water or surface runoff to surface water could occur. Therefore, when possible, samples should be collected based on routes of potential transport. For cases in which contamination has not yet reached points of human exposure but may be transported to those areas in the future, sampling between the contaminant source and the exposure locations should be conducted to help evaluate potential future concentrations to which individuals may be exposed (e.g., through modeling). (See Chapter 6 for additional discussion on contaminant transport.)

4.5.2 SOIL

Soil represents a medium of direct contact exposure and often is the main source of contaminants released into other media. As such, the number, location, and type of samples collected from soils will have a significant effect on the risk assessment. See the box on this page for guidance that provides additional detailed information concerning soil sampling, including information on sampling locations, general soil and vegetation conditions, and sampling equipment, strategies, and techniques. In addition to the general sampling considerations discussed previously, the following specific issues related to soil sampling are discussed below: the heterogeneous nature of soils, designation of hot spots, depth of samples, and fate and transport properties.

SOIL SAMPLING GUIDANCE

Test Methods for Evaluating Solid Waste (SW-846): Physical/Chemical Methods (EPA 1986a)

Field Manual for Grid Sampling of PCB Spill Sites to Verify Cleanups (EPA 1986b)

A Compendium of Superfund Field Operations Methods (EPA 1987c)

Soil Sampling Quality Assurance Guide (EPA Review Draft 1989b)

Heterogeneous nature of soils. One of the largest problems in sampling soil (or other solid materials) is that its generally heterogeneous nature makes collection of representative samples difficult (and compositing of samples virtually impossible -- see Section 4.6.3). Therefore, a large number of soil samples may be required to obtain sufficient data to calculate an exposure concentration. Composite samples sometimes are collected to obtain a more homogeneous sample of a particular area; however, as discussed in a later section, compositing samples also serves to mask contaminant hot spots (as well as areas of low contaminant concentration).

Designation of hot spots. Hot spots (i.e., areas of very high contaminant concentrations) may have a significant impact on direct contact exposures. The sampling plan should consider characterization of hot spots through extensive sampling, field screening, visual observations, or a combination of the above.

Depth of samples. Sample depth should be applicable for the exposure pathways and contaminant transport routes of concern and should be chosen purposively within that depth interval. If a depth interval is chosen purposively, a random procedure to select a sampling point may be established. Assessment of surface exposures will be more certain if samples are collected from the shallowest depth that can be practically obtained, rather than, for example, zero to two feet. Subsurface soil samples are important, however, if soil disturbance is likely or if leaching of chemicals to ground water is of concern, or if the site has current or potential agricultural uses.

Fate and transport properties. The sampling plan should consider physical and chemical characteristics of soil that are important for evaluating fate and transport. For example, soil samples being collected to identify potential sources of ground-water contamination must be able to support models that estimate both quantities of chemicals leaching to ground water and the time needed for chemicals to leach to and within the ground water.

4.5.3 GROUND WATER

Considerable expense and effort normally are required for the installation and development of monitoring wells and the collection of ground-water samples. Wells must not introduce foreign materials and must provide a representative hydraulic connection to the geologic formations of interest. In addition, ground-water samples need to be collected using an approach that adequately defines the contaminant plume with respect to potential exposure points. Existing potential exposure points (e.g., existing drinking water wells) should be sampled.

More detailed information concerning ground-water sampling considerations (e.g., sampling equipment, types, and techniques) can be found in the references in the box on this page. In addition to the general sampling considerations discussed previously in Section 4.5.1, those specific for ground water -- hydrogeologic properties, well location and depth, and filtered vs. unfiltered samples -- are discussed below.

GROUND-WATER SAMPLING GUIDANCE

Practical Guide to Ground-water Sampling (EPA 1985a)

A Compendium of Superfund Field Operations Methods (EPA 1987c)

Handbook: Ground Water (EPA 1987d)

Statistical Methods for Evaluating Ground Water from Hazardous Waste Facilities (EPA 1988b)

Guidance on Remedial Actions for Contaminated Ground Water at Superfund Sites (EPA 1988e)

Ground-water Sampling for Metals Analyses (EPA 1989d)

Hydrogeologic properties. The extent to which the hydrogeologic properties (e.g., hydraulic conductivity, porosity, bulk density, fraction organic carbon, productivity) of the aquifer(s) are characterized may have a significant effect on the risk assessment. The ability to estimate future exposure concentrations depends on the extent to which hydrogeologic properties needed to evaluate contaminant migration are quantified. Repetitive sampling of wells is necessary to obtain samples that are unaffected by drilling and well development and that accurately reflect hydrogeologic properties of the aquifer(s).

Well location and depth. The location of wells should be such that both the horizontal and vertical extent of contamination can be characterized. Separate water-bearing zones may have different aquifer classifications and uses and therefore may need to be evaluated separately in the risk assessment. In addition, sinking or floating layers of contamination may be present at different depths of the wells.

Filtered vs. unfiltered samples. Data from filtered and unfiltered ground-water samples are useful for evaluating chemical migration in ground

water, because comparison of chemical concentrations in unfiltered versus filtered samples can provide important information on the form in which a chemical exists in ground water. For instance, if the concentration of a chemical is much greater in unfiltered samples compared to filtered samples, it is likely that the majority of the chemical is sorbed onto particulate matter and not dissolved in the ground water. This information on the form of chemical (i.e., dissolved or suspended on particulate matter) is important to understanding chemical mobility within the aquifer.

If chemical analysis reveals significantly different concentrations in the filtered and unfiltered samples, try to determine whether there is a high concentration of suspended particles or if apparently high concentrations are due to sampling or well construction artifacts. Supplementary samples can be collected in a manner that will minimize the influence of these artifacts. In addition, consider the effects of the following.

- Filter size. A 0.45 um filter may screen out some potentially mobile particulates to which contaminants are absorbed and thus under-represent contaminant concentrations. (Recent research suggests that a 1.0 um may be a more appropriate filter size.)

- Pumping velocity. Pumping at too high a rate will entrain particulates (to which contaminants are absorbed) that would not normally be mobile; this could overestimate contaminant concentrations.

- Sample oxidation. After contact with air, many metals oxidize and form insoluble compounds that may be filtered out; this may underestimate inorganic chemical concentrations.

- Well construction materials. Corrosion may elevate some metal concentrations even in stainless steel wells.

If unfiltered water is of potable quality, data from unfiltered water samples should be used to estimate exposure (see Chapter 6). The RPM should ultimately decide the type of samples that are collected. If only one type of sample is collected (e.g., unfiltered), justification for not collecting the other type of sample (e.g., filtered) should be provided in the sampling plan.

4.5.4 SURFACE WATER AND SEDIMENT

Samples need to be collected from any nearby surface water body potentially receiving discharge from the site. Samples are needed at a sufficient number of sampling points to characterize exposure pathways, and at potential discharge points to the water body to determine if the site (or some other source) is contributing to surface water/sediment contamination. Some important considerations for surface water/sediment sampling that may affect the risk assessment for various types and portions of water bodies (i.e., lotic waters, lentic waters, estuaries, sediments) are discussed below. More detailed information concerning surface water and sediment sampling, such as selecting sampling locations and sampling equipment, types, and techniques, is provided in the references given in the box below.

SURFACE WATER AND SEDIMENT SAMPLING GUIDANCE

Procedures for Handling and Chemical Analysis of Sediment and Water Samples (EPA and COE 1981)

Sediment Sampling Quality Assurance User's Guide (EPA 1984)

Methods Manual for Bottom Sediment Sample Collection (EPA 1985b)

A Compendium of Superfund Field Operations Methods (EPA 1987c)

An Overview of Sediment Quality in the United States (EPA 1987e)

Proposed Guide for Sediment Collection, Storage, Characterization and Manipulation (The American Society for Testing and

Lotic waters. Lotic waters are fast-moving waters such as rivers and streams. Variations in mixing across the stream channel and downstream in rivers and streams can make it difficult to obtain representative samples. Although the selection of sampling points will be highly dependent on the exposure pathways of concern for a particular site, samples generally should be taken both toward the middle of the channel where the majority of the flow occurs and along the banks where flow is generally lower. Sampling locations should be downgradient of any possible contaminant sources such as tributaries or effluent outfalls. Any facilities (e.g., dams, wastewater treatment plants) upstream that affect flow volume or water quality should be considered during the timing of sampling. "Background" releases upstream could confound the interpretation of sampling results by diluting contaminants or by increasing contaminant loads. In general, sampling should begin downstream and proceed upstream.

Lentic waters. Lentic waters are slow-moving waters such as lakes, ponds, and impoundments. In general, lentic waters require more samples than lotic waters because of the relatively low degree of mixing of lentic waters. Thermal stratification is a major factor to be considered when sampling lakes. If the water body is stratified, samples from each layer should be obtained. Vertical composites of these layers then may be made, if appropriate. For small shallow ponds, only one or two sample locations (e.g., the intake and the deepest points) may be adequate depending on the exposure pathways of concern for the site. Periodic release of water should be considered when sampling impoundments, as this may affect chemical concentrations and stratification.

Estuaries. Contaminant concentrations in estuaries will depend on tidal flow and salinity-stratification, among other factors. To obtain a representative sample, sampling should be conducted through a tidal cycle by taking three sets of samples on a given day: (1) at low tide; (2) at high tide; and (3) at "half tide." Each layer of salinity should be sampled.

Sediments. Sediment samples should be collected in a manner that minimizes disturbance of the sediments and potential contamination of subsequent samples. Sampling in flowing waters should begin downstream and end upstream. Wading should be avoided. Sediments of different composition (i.e., mud, sand, rock) should not be composited. Again, it is important to obtain data that will support the evaluation of the potential exposure pathways of concern. For example, for pathways such as incidental ingestion, sampling of near-shore sediments may be important; however, for dermal absorption of sediment contaminants during recreational use such as swimming, samples from different points throughout the water body may be important. If ingestion of benthic (bottom-dwelling) species or surface water will be assessed during the risk assessment, sediment should be sampled so that characteristics needed for modeling (e.g., fraction of organic carbon, particle size distribution) can be determined (see Section 4.3).

4.5.5 AIR

Guidance for developing an air sampling plan for Superfund sites is provided in *Procedures for Dispersion Modeling and Air Monitoring for Superfund Air Pathway Analysis* (EPA 1989e). That document is Volume IV of a series of four technical guidance manuals called *Procedures for Conducting Air Pathway Analyses for Superfund Applications* (EPA 1989e-h). The other three volumes of the series include discussions of potential air pathways, air emission sources, and procedures for estimating potential source emission rates associated with both the baseline site evaluation and remedial activities at the site.

Air monitoring information, along with recommendations for proper selection and application of air dispersion models, is included in Volume IV. The section on air monitoring contained in this volume presents step-by-step procedures to develop, conduct, and evaluate the results of air concentration monitoring to characterize downwind exposure conditions from Superfund air emission sources. The first step addressed is the process of collecting and reviewing existing air monitoring information relevant to the specific site, including source, receptor, and environmental data. The second step involves determining the level of sophistication for the air monitoring program; the levels range from simple screening procedures to refined techniques.

Selection of a given level will depend on technical considerations (e.g., detection limits) and available resources. The third step on air monitoring is development of the air monitoring plan and includes determination of the type of air monitors, the number and location of monitors, the frequency and duration of monitoring, sampling and analysis procedures, and QA/QC procedures. Step four details the day-to-day activities related to conducting the air maintenance and calibration, and documentation of laboratory results and QA/QC procedures. The fifth and final step involves the procedures necessary to (1) summarize and evaluate the air monitoring results for validity, (2) summarize the statistics used, (3) determine site-related air concentrations (by comparison of upwind and downwind concentrations), and (4) estimate uncertainties in the results related to the monitoring equipment and program and the analytical techniques used in the laboratory.

Given the difficulties of collecting sufficient air samples to characterize both temporal and spatial variability of air concentrations, modeling -- along or in conjunction with monitoring -- is often used in the risk assessment. For the most efficient sampling program, the section in Volume IV on modeling should be used in conjunction with the section on monitoring.

Volume IV also contains a comprehensive bibliography of other sources of air monitoring and modeling guidance. Note, however, that while this volume contains an extensive discussion on planning and conducting air sampling, it does not provide details concerning particular monitoring equipment and techniques. The box on this page lists some sources of detailed information on air sampling. The following paragraphs address several specific aspects of air sampling: temporal and spatial considerations, emission sources, meteorological conditions.

Temporal and spatial considerations. The goal of air sampling at a site is to adequately characterize air-related contaminant exposures. At a minimum, sampling results should be adequate for predictive short-term and long-term modeling. When evaluating long-term inhalation exposures, sample results should be representative of the long-term average air concentrations at the long-term modeling. When evaluating long-term inhalation exposures, sample results should be representative of the long-term average air concentrations at the long-term exposure points. This requires an air sampling plan of sufficient temporal scale to encompass the range of meteorological and climatic conditions potentially affecting emissions, and of sufficient spatial scale to characterize associated air concentrations at potential exposure points. If acute or subchronic exposures resulting from episodes of unusually large emissions are of interest, sampling over a much smaller time scale would be needed.

AIR SAMPLING GUIDANCE

Technical Assistance Document for Sampling and Analysis of Toxic Organic Compounds in Ambient Air (EPA 1983)

A Compendium of Superfund Field Operations Methods (EPA 1987c)

Procedures for Dispersion Modeling and Air Monitoring for Superfund Air Pathway Analysis (EPA 1988f)

Emission sources. Selection of the appropriate type of air monitor will depend on the emission source(s) being investigated as well as the exposure routes to be evaluated. For example, if inhalation of dust is an exposure pathway of concern, then the monitoring equipment must be able to collect respirable dust samples.

Meteorological conditions. Site-specific meteorological conditions should be obtained (e.g., from the National Weather Service) or recorded during the air sampling program with sufficient detail and quality assurance to substantiate and explain the air sampling results. The review of these meteorological data can help indicate the sampling locations and frequencies. Meteorological characteristics also will be necessary if air modeling is to be conducted.

4.5.6 BIOTA

Organisms sampled for human health risk assessment purposes should be those that are likely to be consumed by humans. This may include animals such as commercial and game fish (e.g., salmon, trout, catfish), shellfish (e.g., oysters, clams, crayfish), fowl (e.g., pheasant, duck), and terrestrial mammals (e.g., rabbit, deer), as well as plants such as grains (e.g., wheat, corn), vegetables (e.g., spinach, carrots), and fruit (e.g., melons, strawberries). An effort should be made to sample species that are consumed most frequently by humans. Guidance for collecting biota samples is provided in the references given in the box below. The following paragraphs address the following special aspects of biota sampling: portion vs. whole sampling, temporal concerns, food preference, fish sampling, involvement by other agencies.

BIOTA SAMPLING GUIDANCE

Food and Drug Administration's *Pesticide Analytical Manual* (FDA 1977)

Cooperative Agreement on the Monitoring of Contaminants in Great Lakes Sport Fish for Human Health Purposes (EPA 1985c)

FDA's *Pesticides and Industrial Chemicals in Domestic Foods* (FDA 1986)

A Compendium of Superfund Field Operations Methods (EPA 1987c)

Guidance Manual for Assessing Human Health Risks from Chemically Contaminated Fish and Shellfish (EPA 1989i)

Portion vs. whole sampling. If only human exposure is of concern, chemical concentrations should be measured only in edible portion(s) of the biota. For many fish species, estimates of concentrations in fillets (skin on or skin off) are the most appropriate measures of exposure concentrations. Whole body measurements may be needed, however, for certain species of fish and/or for environmental risk assessments. For example, for some species, especially small ones (e.g., smelt), whole body concentrations are most appropriate. (See *Risk Assessment Guidance for Superfund: Environmental Evaluation Manual* (EPA 1989a) for more information concerning biota sampling for environmental assessment.) The edible portion of an organism can vary with species and with the potentially exposed subpopulation.

Temporal concerns. Any conditions that may result in non-representative sampling, such as sampling during a species' migration or when plants are not in season, should be avoided.

Food preferences. At some sites, human subpopulations in the area may have different food consumption patterns that need to be evaluated. For example, some people commonly eat the hepatopancreas of shellfish. In these cases, organ concentrations would be most appropriate for estimating exposure. Another example of a less common food preference is consumption of relatively large quantities of seaweed and other less commonly eaten seafoods in some Asian communities.

Fish sampling. It is recommended that fish of "catchable" size be sampled instead of young, small fish because extremely young fish are not likely to be consumed. Older, larger fish also generally are more likely to have been exposed to site-specific contaminants for a long time, although for some species (e.g., salmon) the reverse is true. Both bottom-dwelling (benthic) and open-water species should be sampled if both are used as a food source.

Other agencies. Biota sampling may involve other federal agencies such as the Fish and Wildlife Service or the Department of Agriculture. The equivalent state agencies also may be involved. In such cases, these agencies should be involved early in the scoping process.

4.6 DEVELOPING AN OVERALL STRATEGY FOR SAMPLE COLLECTION

For each medium at a site, there are several strategies for collecting samples. The sampling strategies for a site must be appropriate for use in

a quantitative risk assessment; if inappropriate, even the strictest QA/QC procedures associated with the strategy will not ensure the usability of sample results. Generally, persons actually conducting the field investigation will determine the strategy. As discussed in Section 4.1, risk assessors also should be involved in discussions concerning the strategy. The following areas of major concern (from a risk assessment perspective) are discussed in this section: sample size, sampling location, types of samples, temporal and meteorological factors, field analyses, and cost of sampling. Many of these areas also are discussed for specific media in Section 4.5. See the box in the opposite column and Section 4.5 for more detailed guidance on sampling strategy.

4.6.1 DETERMINE SAMPLE SIZE

Typically, sample size and sample location (see Section 4.6.2) are determined at the same time. Therefore, much of the discussion in this subsection is also pertinent to determining sampling location. The discussion on statistics in Section 4.4 is useful for both sample size and location determinations.

A number of considerations are associated with determining an appropriate number of samples for a risk assessment. These considerations include the following four factors:

(1) number of areas of concern that will be sampled;

(2) statistical methods that are planned;

(3) statistical performance (i.e., variability power, and certainty) of the data that will be collected; and

(4) practical considerations of logistics and cost.

In short, many decisions must be made by the risk assessor related to the appropriate sample size for an investigation. A statistician cannot estimate an appropriate sample size without the supporting information provided by a risk assessor. The following paragraphs discuss these four factors as they relate to sample size determinations.

Areas of concern. A major factor that influences how many samples are appropriate is the number of areas of concern that are established prior to sampling. As discussed in the next subsection, if more areas of concern are identified, then more samples generally will be needed to characterize the site. If the total variability in chemical concentrations is reduced substantially by subdividing the site into areas of concern, then the statistical performance should improve and result in a more accurate assessment of the site.

SAMPLING STRATEGY GUIDANCE

Test Methods for Evaluating Solid Waste (SW-846): Physical/Chemical Methods (EPA 1986a)

Data Quality Objectives for Remedial Response Activities: Development Process (EPA 1987a)

Data Quality Objectives for Remedial Response Activities: Example Scenario: RI/FS Activities at a Site with Contaminated Soils and Ground Water (EPA 1987b)

Expanded Site Inspection (ESI) Transitional Guidance for FY 1988 (EPA 1987f)

Quality Assurance Field Operations Manual (EPA 1987g)

Statistical Methods for Evaluating the Attainment of Superfund Cleanup Standards: Volume 1, Soils and Solid Media (EPA 1988f)

Proposed Guidelines for Exposure-related Measurements (EPA 1988g)

Interim Report on Sampling Design Methodology (EPA 1988h)

Standard Handbook of Hazardous Waste Treatment and Disposal (Freeman 1989)

Soil Sampling Quality Assurance Guide (EPA

Statistical methods. A variety of statistical manipulations may need to be performed on the data used in the risk assessment. For example, there may be comparisons with background

concentrations, estimates of upper confidence limits on means, and determinations of the probability of identifying hot spots. Each of these analyses requires different calculations for determining a sample size that will yield a specified statistical performance. Some of the available guidance, such as the Ground-water Monitoring guidance (EPA 1986c), the RCRA Delisting guidance (EPA 1985d), and the Soils Cleanup Attainment guidance (EPA 1988f), address these strategies in detail.

Statistical performance (i.e., variability, power, and certainty). If samples will be taken from an area that is anticipated to have a high degree of variability in chemical concentrations, then many samples may be required to achieve a specified level of certainty and power. If contaminant concentrations in an area are highly variable and only a few samples can be obtained, then the risk assessor should anticipate (1) a great deal of uncertainty in estimating mean concentrations at the site, (2) difficulty in defining the distribution of the data (e.g., normal), and (3) upper confidence limits much higher than the mean. Identification of multiple areas of concern -- each with its own set of samples and descriptive statistics -- will help reduce the total variability if the areas of concern are defined so that they are very different in their contaminant concentration profiles. Risk assessors should discuss in the scoping meeting both the anticipated variability in the data and the desired power and certainty of the statistics that will be estimated from the data.

As discussed in Section 4.4.3, power is the likelihood of detecting a false null hypothesis. Power is particularly important when comparing site characteristics with background. For example, if a 10 percent difference in mean concentrations needs to be determined with 99 percent likelihood (i.e., power of 0.99), a very large number of samples will likely be needed (unless the site and background variabilities are extremely low). On the other hand, if the investigator is only interested in whether the onsite average conditions are 100 times larger than background or can accept a lower chance of detecting the difference if it exists (i.e., a lower power), then a smaller sample size could be accommodated.

The other statistical performance quantity besides power that may need to be specified is the certainty of the calculations. One minus the certainty is the significance level (i.e., α), or false positive rate (see also Section 4.4.3). The higher the desired certainty level (i.e., the lower the significance level), the greater the true difference must be to observe a statistical difference. In the case of upper confidence limits on estimates of mean concentrations, the higher the desired certainty level, the higher will be the upper confidence limit. This follows from the fact that in general, as certainty increases (i.e., α becomes smaller), the size of the confidence interval also increases.

Practical considerations. Finally, questions of practicality, logistics, sampling equipment, laboratory constraints, quality assurance, and cost influence the sample size that will be available for data analysis. After the ideal sample size has been determined using other factors, practical considerations can be introduced to modify the sample size if necessary.

4.6.2 ESTABLISH SAMPLING LOCATIONS

There are three general strategies for establishing sample locations: (1) purposive, (2) completely random, and (3) systematic. Various combinations of these general strategies are possible and acceptable.

Much of the discussion on statistics in the preceding subsection and in Section 4.4 is appropriate here. Typically, a statistician should be consulted when determining sampling location.

Purposive sampling. Although areas of concern are established purposively (e.g., with the intention of identifying contamination), the sampling locations within the areas of concern generally should not be sampled purposively if the data are to be used to provide defensible information for a risk assessment. Purposively identified sampling locations are not discouraged if the objective is site characterization, conducting a chemical inventory, or the evaluation of visually obvious contamination. The sampling results, however, may overestimate or underestimate the true conditions at the site depending on the strategies of the sampling team. Due to the bias associated with the samples, data from purposively

identified sampling locations generally should not be averaged, and distributions of these data generally should not be modeled and used to estimate other relevant statistics. After areas of concern have been established purposively, ground-water monitoring well locations, continuous air monitor locations, and soil sample locations should be determined randomly or systematically within the areas of concern.

Random sampling. Random sampling involves selecting sampling locations in an unbiased manner. Although the investigator may have chosen the area of concern purposively, the location of random sampling points within the area should be independent of the investigator (i.e., unbiased). In addition, the sampling points should be independent of each other; that is, it should not be possible to predict the location of one sampling point based on the location of others. Random sampling points can be established by choosing a series of pairs of random numbers that can be mapped onto a coordinate system that has been established for each area of concern.

Several positive features are associated with data collected in a random sampling program. First, the data can be averaged and used to estimate average concentrations for the area of concern (rather than simply an average of the samples that were acquired). Second, estimates of the uncertainty of the average and the distributional form of the concentration measurements are informative and simple to estimate when they are determined from data that were obtained randomly. Finally, if there is a trend or systematic behavior to the chemical concentrations (e.g., sampling is occurring along a chemical gradient), then random sampling is preferred because it reduces the likelihood that all of the high concentration locations are sampled to the exclusion of the low concentration locations.

Systematic sampling. Systematic sample locations are established across an area of concern by laying out a grid of sampling locations that follow a regular pattern. Systematic sampling ensures that the sampling effort across the area of concern is uniform and that samples are collected in each area. The sampling location grid should be determined by randomly identifying a single initial location from which the grid is constructed. If such a random component is not introduced, the sample is essentially purposive. The grid can be formed in several patterns including square, rectangular, triangular, or hexagonal, depending on the shape of the area. A square pattern is often the simplest to establish. Systematic sampling is preferable to other types of sampling if the objective is to search for small areas with elevated concentrations. Also, geostatistical characterizations -- as described in the DQO guidance (EPA 1987a,b) -- are best done with data collected from a systematic sample.

Disadvantages of systematic sampling include the need for special variance calculations in order to estimate confidence limits on the average concentration. The Soils Cleanup Attainment guidance (EPA 1988f) discusses these calculations in further detail.

4.6.3 DETERMINE TYPES OF SAMPLES

Another item of concern is the determination of the types of samples to be collected. Basically, two types of samples may be collected at a site: grab and composite.

Grab samples. Grab samples represent a single unique part of a medium collected at a specific location and time.

Composite samples. Composite samples -- sometimes referred to as continuous samples for air -- combine subsamples from different locations and/or times. As such, composite samples may dilute or otherwise misrepresent concentrations at specific points and, therefore, should be avoided as the only inputs to a risk assessment. For media such as soil, sediment, and ground water, composite samples generally may be used to assess the presence or absence of contamination; however, they may be used in risk assessment only to represent average concentrations (and thus exposures) at a site. For example, "hot spots" cannot be determined using composite samples. For surface water and air, composite samples may be useful if concentrations and exposures are expected to vary over time or space, as will often be the case in a large stream or river. Composites then can be used to estimate daily or monthly average concentrations, or to account for

stratification due to depth or varying flow rates across a stream.

4.6.4 CONSIDER TEMPORAL AND METEOROLOGICAL FACTORS

Temporal (time) and meteorological (weather) factors also must be considered when determining sampling strategies. The sampling design should account for fluctuations in chemical concentrations due to these factors because in general, the variability in sampling results increases with increasing complexity of these factors. When these factors are complex, specialized and detailed sampling designs are needed to maintain a constant and certain level of accuracy in the results. Countering this need, however, is the cost of the sampling. The following paragraphs address the interactions of the single sampling event, annual/seasonal sampling cycle, variability estimation, and the cost of sampling.

Single sampling event. Variability measures from a single sampling event will underestimate the overall variability of concentrations across an area of concern, which in turn will result in the underestimation of the confidence limits on the mean. The reason for this underestimation is that temporal variability is not included in an evaluation of the total environmental variability at the site.

Annual/seasonal sampling cycle. The ideal sampling strategy incorporates a full annual sampling cycle. If this strategy cannot be accommodated in the investigation, at least two sampling events should be considered. These sampling events should take place during opposite seasonal extremes. For example, sampling periods that may be considered extremes in temporal sampling include (1) high water/low water, (2) high recharge/low recharge, (3) windy/calm, and (4) high suspended solids/clear water. This type of sampling requires some prior knowledge of regional seasonal dynamics. In addition, a sampling team that can mobilize rapidly might be needed if the particular year of sampling is not typical and the extreme conditions occur at an unusual time. See the box on this page for examples of seasonal variability.

Variability estimation. The simple variance estimators that are often used in risk assessment require that the data are independent or uncorrelated. Certain types of repeated samples, however, (e.g., those from ground-water wells or air monitors) actually are time series data that might be correlated. In other words, the concentration of a contaminant in an aquifer measured at a well on a given day will depend, in part, on what the concentration in the aquifer was on the previous day. To reduce this dependence (e.g., due to seasonal variability), sampling of ground-water wells and air monitors should be either separated in time or the data should be evaluated using statistical models with variance estimators that can accommodate a correlation structure. Otherwise, if time series data that are correlated are treated as a random sample and used to calculate upper confidence limits on the mean, the confidence limits will be underestimated.

SEASONAL VARIABILITY

Regardless of the medium sampled, sample composition may vary depending on the time of year and weather conditions when the sample is collected. For example, rain storms may greatly alter soil composition and thus affect the types and concentrations of chemicals present on solid material; heavy precipitation and runoff from snowmelt may directly dilute chemical concentrations or change the types of chemicals present in surface water; heavy rain also may result in sediment loading to water bodies, which could increase contamination or affect the concentrations of other contaminants through adsorption and settling in the water column; if ground-water samples are collected from an area heavily dependent on ground water for irrigation, the composition of a sample collected during the summer growing season may greatly differ from the composition of a sample collected in the winter.

Ideally, samples of various media should be collected in a manner that accounts for time and weather factors. If seasonal fluctuations cannot be characterized in the investigations, details concerning meteorological, seasonal, and climatic conditions during sampling must be documented.

4.6.5 USE FIELD SCREENING ANALYSES

An important component of the overall sampling strategy is the use of field screening analyses. These types of analyses utilize instruments that range from relatively simple (e.g., hand-held organic vapor detectors) to more sophisticated (e.g., field gas chromatographs). (See *Field*

Screening Methods Catalog [EPA 1987h] for more information.) Typically, field screening is used to provide threshold indications of contamination. For example, on the basis of soil gas screening, the field investigation team may determine that contamination of a particular area is indicated and therefore detailed sampling is warranted. Although field screening results usually are not directly used in the risk assessment, they are useful for streamlining sampling and the overall RI/FS process.

4.6.6 CONSIDER TIME AND COST OF SAMPLING

Two primary constraints in sampling are time and cost. Time consuming or expensive sampling strategies for some media may prohibit multiple sampling points. For example, multiple ground-water wells and air monitors on a grid sampling pattern are seldom located within a single area of concern. However, multiple surface water and soil samples within each area of concern are easier to obtain. In the case of ground water and air, several areas of concern may have to be collapsed into a single area so that multiple samples will be available for estimating environmental variability or so that the dynamics of these media can be evaluated using accepted models of fate and transport.

In general, it is important to remember when developing the sampling strategy that detailed sampling must be balanced against the time and cost involved. The goal of RI/FS sampling is not exhaustive site characterization, but rather to provide sufficient information to form the basis for site remediation.

4.7 QA/QC MEASURES

This section presents an overview of the following quality assurance/quality control (QA/QC) considerations that are of particular importance for risk assessment sampling: sampling protocol, sampling devices, QC samples, collection procedures, and sample preservation. Note, however, that the purpose of this discussion is to provide background information; the risk assessor will not be responsible for most QA/QC evaluations.

The *Quality Assurance Field Operations Manual* (EPA 1987g) should be reviewed. In addition, the EPA Environmental Monitoring Support Laboratory in Las Vegas, Nevada, (EMSL-LV) currently is writing a guidance document concerning the development of quality assurance sample designs for Superfund site investigations. Regional QA/QC contacts (e.g., the regional Environmental Services Division) or EMSL-LV should be consulted if more information concerning QA/QC procedures for sampling is desired.

4.7.1 SAMPLING PROTOCOL

The sampling protocol for a risk assessment should include the following:

- objectives of the study;
- procedures for sample collection, preservation, handling, and transport; and
- analytical strategies that will be used.

Presenting the objectives of the RI sampling is particularly important because these objectives also will determine the focus of the risk assessment. There should be instructions on documenting conditions present during sampling (e.g., weather conditions, media conditions). Persons collecting samples must be adequately trained and experienced in sample collection. Test evaluations of the precision attained by persons involved in sample collection should be documented (i.e., the individual collecting a sample should do so in a manner that ensures that a homogeneous, valid sample is reproducibly obtained). The discussion of analytical strategies should specify quantitation limits to be achieved during analyses of each medium.

4.7.2 SAMPLING DEVICES

The devices used to collect, store, preserve, and transport samples must not alter the sample in any way (i.e., the sampling materials cannot be reactive, sorptive, able to leach analytes, or cause interferences with the laboratory analysis). For example, if the wrong materials are used to construct wells for the collection of ground-water samples, organic chemicals may be adsorbed to the well materials and not be present in the collected sample.

4.7.3 QC SAMPLES

Field QC samples (e.g., field blanks, trip blanks, duplicates, split samples) must be collected, stored, transported, and analyzed in a manner identical to those for site samples. The meaning and purpose of blank samples are discussed in detail in Chapter 5. Field duplicate samples are usually two samples collected simultaneously from the same sampling location and are used as measures of either the homogeneity of the medium sampled in a particular location or the precision in sampling. Split samples are usually one sample that is divided into equal fractions and sent to separate independent laboratories for analysis. These split samples are used to check precision and accuracy of laboratory analyses. Samples may also be split in the same laboratory, which can provide information on precision. The laboratory analyzing the samples should not be aware of the identity of the field QC samples (e.g., labels on QC samples should be identical to those on the site samples).

4.7.4 COLLECTION PROCEDURES

Collection procedures should not alter the medium sampled. The general environment surrounding the location of the sample should remain the same so that the collected samples are representative of the situation due to the site conditions, not due to conditions posed by the sampling equipment.

4.7.5 SAMPLE PRESERVATION

Until analysis by the laboratory, any chemicals in the samples must be maintained as close to the same concentrations and identities as in the environment from which they came. Therefore, special procedures may be needed to preserve the samples during the period between collection and analysis.

4.8 SPECIAL ANALYTICAL SERVICES

EPA's SAS, operated by the CLP, may be necessary for two main reasons: (1) the standard laboratory methods used by EPA's Routine Analytical Services (RAS) may not be appropriate (e.g., lower detection limits may be needed),[4] and (2) chemicals other than those on the target compound list (TCL; i.e., chemicals usually analyzed under the Superfund program) may be suspected at the site and therefore may need to be analyzed. A discussion on the RAS detection limits is provided in Chapter 5. Additional information on SAS can be found in the *User's Guide to the Contract Laboratory Program* (EPA 1988i).

In reviewing the historical data at a site, the risk assessor should determine if non-TCL chemicals are expected. As indicated above, non-TCL chemicals may require special sample collection and analytical procedures using SAS. Any such needs should be discussed at the scoping meeting. SAS is addressed in greater detail in Chapter 5.

4.9 TAKING AN ACTIVE ROLE DURING WORKPLAN DEVELOPMENT AND DATA COLLECTION

The risk assessor should be sure to take an active role during workplan development and data collection. This role involves three main steps:

(1) present risk assessment sampling needs at the scoping meeting;

(2) contribute to the workplan and review the Sampling and Analysis Plan; and

(3) conduct interim reviews of outputs of the field investigation.

See Chapter 9 for information on the role of the RPM during workplan development and data collection.

4.9.1 PRESENT RISK ASSESSMENT SAMPLING NEEDS AT SCOPING MEETING

At the scoping meeting, the uses of samples and data to be collected are identified, strategies for sampling and analysis are developed, DQOs are established, and priorities for sample collection are assigned based on the importance of

the data in meeting RI/FS objectives. One of the RI/FS objectives, of course, is the baseline risk assessment. Therefore, the risk assessment data needs and their fit with those of other RI/FS components are discussed. If certain risk assessment sampling needs are judged infeasible by the scoping meeting attendees, all persons involved with site investigation should be made aware of the potential effects of exclusion on the risk assessment.

4.9.2 CONTRIBUTE TO WORKPLAN AND REVIEW SAMPLING AND ANALYSIS PLAN

The outcome of the scoping meeting is the development of a workplan and a SAP. The workplan documents the decisions and evaluations made during the scoping process and presents anticipated future tasks, while the SAP specifies the sampling strategies, the numbers, types, and locations of samples, and the level of quality control. The SAP consists of a quality assurance project plan (QAPjP) and a field sampling plan (FSP). Elements of the workplan and the SAP are discussed in detail in Appendix B of the RI/FS guidance (EPA 1988a). Both the workplan and the SAP generally are written by the personnel who will be involved in the collection of the samples; however, these documents should be reviewed by all personnel who will be using the resulting sample data.

Review the workplan. The workplan should describe the tasks involved in conducting the risk assessment. It also should describe the development of a preliminary assessment of public health and environmental impacts at the site. The risk assessor should review the completed workplan to ensure that all feasible risk assessment sampling needs have been addressed as discussed in the scoping meeting. In particular, this review should focus on the descriptions of tasks related to:

- field investigation (e.g., source testing, media sampling), especially with respect to
  - -- background concentrations by medium,
  - -- quantification of present and future exposures, e.g.,
    - exposure pathways
    - present and potential future land use
    - media that are or may be contaminated
    - locations of actual and potential exposure
    - present concentrations at appropriate exposure points,
  - -- data needs for statistical analysis of the above, and
  - -- data needs for fate and transport models;
- sample analysis/validation, especially with respect to
  - -- chemicals of concern, and
  - -- analytical quantification levels;
- data evaluation; and
- assessment of risks.

In reviewing the above, the precise information necessary to satisfy the remainder of this guidance should be anticipated.

Review the SAP. The risk assessor should carefully review and evaluate all sections of the SAP to determine if data gaps identified in the workplan will be addressed adequately by the sampling program. Of particular importance is the presentation of the objectives. In the QAPjP component of the SAP, the risk assessor should pay particular attention to the QA/QC procedures associated with sampling (e.g., number of field blanks, number of duplicate samples -- see Section 4.8). The SAP should document the detailed, site-specific procedures that will be followed to ensure the quality of the resulting samples. Special considerations in reviewing the SAP are discussed in Section 4.1.3.

In reviewing the FSP, pay particular attention to the information on sample location and frequency, sampling equipment and procedures, and sample

handling and analysis. As discussed in Section 4.5, the sampling procedures should address:

- each medium of concern;
- background concentrations;
- all potential exposure points within each medium;
- migration to potential exposure points, including data for models;
- potential exposures based on possible future land uses;
- sufficient data to satisfy concerns about distributions of sampling data and statistics; and
- number and location of samples.

The analytical plans in the FSP should be reviewed to ensure that DQOs set during the scoping meeting will be met.

The SAP may be revised or amended several times during the site investigation. Therefore, a review of all proposed changes to the sampling and analysis plan that potentially may affect the data needs for risk assessment is necessary. Prior to any changes in the SAP during actual sampling, compliance of the changes with the objectives of the SAP must be checked. (If risk assessment objectives are not specified in the original SAP, they will not be considered when changes to an SAP are proposed.)

4.9.3 CONDUCT INTERIM REVIEWS OF FIELD INVESTIGATION OUTPUTS

All sampling results should be reviewed as soon as they are available to determine if the risk assessment data needs outlined in the workplan have been met by the sampling. Compare the actual number, types, and locations of samples collected with those planned in the SAP. Sampling locations frequently are changed in the field when access to a planned sampling location is obstructed. The number of samples collected may be altered if, for instance, there is an insufficient amount of a certain medium to collect the planned number of samples (e.g., if several wells are found to be dry).

If certain sampling needs have not been met, then the field investigators should be contacted to determine why these samples were not collected. If possible, the risk assessor should obtain samples to fill these data gaps. If time is critical, Special Analytical Services (see Section 4.7) may be used to shorten the analytical time. If this is not possible, then the risk assessor should evaluate all sampling results as discussed in Chapter 5, documenting the potential effect that these data gaps will have on the quantitative risk assessment. In general, the risk assessment should not be postponed due to these data gaps.

ENDNOTES FOR CHAPTER 4

1. Some information that is appropriate for the assessment of human health risks also may be suitable and necessary for an environmental evaluation of the site. Procedures for conducting an environmental evaluation of the hazardous waste site are outlined in the companion volume of this guidance, the Environmental Evaluation Manual (EPA 1989a), and are not discussed in this chapter.

2. The term "media" refers to both environmental media (e.g., soil) and biota (e.g., fish).

3. "Areas of Concern" within the context of this guidance should be differentiated from the same terminology used by the Great Lakes environmental community. This latter use is defined by the International Joint Commission as an area found to be exceeding the Great Lakes Water Quality Agreement objectives.

4. New routine services that provide lower detection limits are currently under development. Contact the headquarters Analytical Operations Branch for further information.

REFERENCES FOR CHAPTER 4

American Society of Testing and Materials (ASTM). Undated. A Proposed Guide for Sediment Collection, Storage, Characterization, and Manipulation. Draft. Available from G. Allen Burton, Dept of Biological Sciences, Wright State University, Dayton, Ohio 45435.

- Provides information concerning how to collect contaminated sediments, sediment spiking, dilution procedures, and QA/QC. Will probably be in the annual ASTM manual.

Environmental Protection Agency (EPA). 1981. Procedures for Handling and Chemical Analysis of Sediment and Water Samples. Great Lakes Laboratory.

Environmental Protection Agency (EPA). 1983. Technical Assistance Document for Sampling and Analysis of Toxic Organic Compounds in Ambient Air. Office of Research and Development.

- Provides guidance to persons involved in designing and implementing ambient air monitoring programs for toxic organic compounds. Includes guidance on selecting sampling/analytical methods, sampling strategy, QA procedures, and data format. Outlines policy issues.

Environmental Protection Agency (EPA). 1984. Sediment Sampling Quality Assurance User's Guide. Environmental Monitoring Support Laboratory. Las Vegas, NV. NTIS: PB-85-233-542.

- Overview of selected sediment models presented as a foundation for stratification of study of regions and selection of locations for sampling sites, methods of sampling, sampling preparation and analysis. Discussion of rivers, lakes, and estuaries.

Environmental Protection Agency (EPA). 1985a. Practical Guide to Ground-water Sampling. Environmental Research Laboratory. Ada, OK. EPA 600/2-85/104.

- Contains information on laboratory and field testing of sampling materials and procedures. Emphasizes minimizing errors in sampling and analysis.

Environmental Protection Agency (EPA). 1985b. Methods Manual for Bottom Sediment Sample Collection. Great Lakes National Program Office. EPA 905/4-85/004.

- Provides guidance on survey planning, sample collection, document preparation, and quality assurance for sediment sampling surveys. Sample site selection, equipment/containers, collection field observation, preservation, handling custody procedures.

Environmental Protection Agency (EPA). 1985c. Cooperative Agreement on the Monitoring of Contaminants in Great Lakes Sport Fish for Human Health Purposes. Region V, Chicago, IL.

- Discusses sampling protocols and sample composition used for sport fish (chinook salmon, coho salmon, lake trout, and rainbow trout), maximum composite samples (5 fish) and length ranges which would be applicable to hazardous waste sites contaminating lakes or streams used for recreational fishing.

Environmental Protection Agency (EPA). 1985d. Petitions to Delist Hazardous Wastes Guidance Manual. Office of Solid Waste. EPA/530/SW-85/003.

Environmental Protection Agency (EPA). 1986a. Test Methods for Evaluating Solid Waste (SW-846): Physical/Chemical Methods. Office of Solid Waste.

- Provides analytical procedures to test solid waste to determine if it is a hazardous waste as defined under RCRA. Contains information for collecting solid waste samples and for determining reactivity, corrosivity, ignitability, composition of waste, and mobility of waste compounds.

Environmental Protection Agency (EPA). 1986b. Field Manual for Grid Sampling of PCB Spill Sites to Verify Cleanups. Office of Toxic Substances. EPA/560/5-86/017.

- Provides detailed, step-by-step guidance for using hexagonal grid sampling; includes sampling design, collection, QA/QC and reporting.

Environmental Protection Agency (EPA). 1986c. Resource Conservation and Recovery Act (RCRA) Ground-water Monitoring Technical Enforcement Guidance Document. Office of Waste Programs Enforcement.

- Contains a detailed presentation of the elements and procedures essential to the design and operation of ground-water monitoring systems that meet the goals of RCRA and its regulations. Includes appendices on statistical analysis and some geophysical techniques.

Environmental Protection Agency (EPA). 1987a. Data Quality Objectives for Remedial Response Activities: Development Process. Office of Emergency and Remedial Response and Office of Waste Programs Enforcement. EPA/540/G-87/003. (OSWER Directive 9335.0-7B).

- Identifies (1) the framework and process by which data quality objectives (DQOs; qualitative and quantitative statements that specify the quality of the data required to support Agency decisions during remedial response activities) are developed and (2) the individuals responsible for development of DQOs. Provides procedures for determining a quantifiable degree of certainty that can be used in making site-specific decisions. Provides a formal approach to integration of DQO development with sampling and analysis plan development. Attempts to improve the overall quality and cost effectiveness of data collection and analysis activities.

Environmental Protection Agency (EPA). 1987b. Data Quality Objectives for Remedial Response Activities: Example Scenario: RI/FS Activities at a Site with Contaminated Soils and Ground Water. Office of Emergency and Remedial Response and Office of Waste Programs Enforcement. EPA/540/G-87/004.

- Companion to EPA 1987a. Provides detailed examples of the process for development of data quality objectives (DQOs) for RI/FS activities under CERCLA.

Environmental Protection Agency (EPA). 1987c. A Compendium of Superfund Field Operations Methods. Office of Emergency and Remedial Response. EPA/540/P-87/001. (OSWER Directive 9355.0-14).

Environmental Protection Agency (EPA). 1987d. Handbook: Ground Water. Office of Research and Development. EPA/625/6-87/016.

- Resource document that brings together the available technical information in a form convenient for personnel involved in ground-water management. Also addresses minimization of uncertainties in order to make reliable predictions about contamination response to corrective or preventative measures.

Environmental Protection Agency (EPA). 1987e. An Overview of Sediment Quality in the United States. Office of Water Regulations and Standards.

- Good primer. Contains many references.

Environmental Protection Agency (EPA). 1987f. Expanded Site Inspection (ESI) Transitional Guidance for FY 1988. Office of Emergency and Remedial Response. (OSWER Directive 9345.1-.02).

- Provides reader with a consolidated ready reference of general methodologies and activities for conducting inspection work on sites being investigated for the NPL.

Environmental Protection Agency (EPA). 1987g. Quality Assurance Field Operations Manual. Office of Solid Waste and Emergency Response.

- Provides guidance for the selection and definition of field methods, sampling procedures, and custody responsibilities.

Environmental Protection Agency (EPA). 1987h. Field Screening Methods Catalog. Office of Emergency and Remedial Response.

- Provides a listing of methods to be used during field screening, and includes method descriptions, their application to particular sites, their limitations and uses, instrumentation requirements, detection limits, and precision and accuracy information.

Environmental Protection Agency (EPA). 1988a. Guidance for Conducting Remedial Investigations and Feasibility Studies Under CERCLA. Interim Final. Office of Emergency and Remedial Response. (OSWER Directive 9355.3-01).

- Provides the user (e.g., EPA personnel, state agencies, potentially responsible parties (PRPs), federal facility coordinators, and contractors assisting in RI/FS-related activities) with an overall understanding of the RI/FS process. Includes general information concerning scoping meetings, the development of conceptual models at the beginning of a site investigation, sampling, and analysis.

Environmental Protection Agency (EPA). 1988b. Statistical Methods for Evaluating Ground Water from Hazardous Waste Facilities. Office of Solid Waste.

- Specifies five different statistical methods that are appropriate for ground-water monitoring. Outlines sampling procedures and performance standards that are designed to help minimize the occurrence of Type I and Type II errors.

Environmental Protection Agency (EPA). 1988c. Surface Impoundment Clean Closure Guidance Manual. Office of Solid Waste.

Environmental Protection Agency (EPA). 1988d. Love Canal Emergency Declaration Area Habitability Study Report. Prepared by CH2M Hill and Life Systems for EPA Region II.

- Provides a formal comparison of samples with background as well as detailed discussions concerning problems associated with sampling to evaluate data.

Environmental Protection Agency (EPA). 1988e. Guidance on Remedial Actions for Contaminated Ground Water at Superfund Sites. Interim Final. Office of Emergency and Remedial Response. (OSWER Directive 9283.1-2).

- Provides guidance to develop, evaluate, and select ground-water remedial actions at Superfund sites, focusing on policy issues and establishing cleanup levels. Also includes discussion of data collection activities for characterization of contamination.

Environmental Protection Agency (EPA). 1988f. Statistical Methods for Evaluating the Attainment of Superfund Cleanup Standards. Volume I: Soils and Solid Media. Draft. Office of Policy, Planning, and Evaluation.

- Provides statistical procedures that can be used in conjunction with attainment objectives defined by EPA to determine, with the desired confidence, whether a site does indeed attain a cleanup standard. It also provides guidance on sampling of soils to obtain baseline information onsite, monitor cleanup operations, and verify attainment of cleanup objectives.

Environmental Protection Agency (EPA). 1988g. Proposed Guidelines for Exposure-related Measurements. 53 Federal Register 48830 (December 2, 1988).

- Focuses on general principles of chemical measurements in various physical and biological media. Assists those who must recommend, conduct, or evaluate an exposure assessment.

Environmental Protection Agency (EPA). 1988h. Interim Report on Sampling Design Methodology. Environmental Monitoring Support Laboratory. Las Vegas, NV. EPA/600/X-88/408.

- Provide guidance concerning the statistical determination of the number of samples to be collected.

Environmental Protection Agency (EPA). 1988i. User's Guide to the Contract Laboratory Program. Office of Emergency and Remedial Response.

Environmental Protection Agency (EPA). 1989a. Risk Assessment Guidance for Superfund: Environmental Evaluation Manual. Interim Final. Office of Emergency and Remedial Response. EPA/540/1-89/001A. (OSWER Directive 9285.7-01).

Environmental Protection Agency (EPA). 1989b. Soil Sampling Quality Assurance Guide. Review Draft. Environmental Monitoring Support Laboratory. Las Vegas, NV.

- Replaces earlier edition: NTIS Pb-84-198-621. Includes DQO's, QAPP, information concerning the purpose of background sampling, selection of numbers of samples and sampling sites, error control, sample design, sample documentation.

Environmental Protection Agency (EPA). 1989c. Statistical Analysis of Ground-water Monitoring Data at RCRA Facilities. Office of Solid Waste.

Environmental Protection Agency (EPA). 1989d. Ground-water Sampling for Metals Analyses. Office of Solid Waste and Emergency Response. EPA/540/4-89-001.

Environmental Protection Agency (EPA). 1989e. Air Superfund National Technical Guidance Series. Volume IV: Procedures for Dispersion Modeling and Air Monitoring for Superfund Air Pathway Analysis. Interim Final. Office of Air Quality Planning and Standards. Research Triangle Park, NC. EPA/450/1-89/004.

- This volume discusses procedures for dispersion modeling and air monitoring for superfund air pathway analyses. Contains recommendations for proper selection and application of air dispersion models and procedures to develop, conduct, and

evaluate the results of air concentration monitoring to characterize downwind exposure conditions from Superfund air emission sources.

Environmental Protection Agency (EPA). 1989f. Air Superfund National Technical Guidance Series. Volume I: Application of Air Pathway Analyses for Superfund Activities. Interim Final. Office of Air Quality Planning and Standards. Research Triangle Park, NC. EPA/450/1-89/001.

- Provides recommended procedures for the conduct of air pathway analyses (APAs) that meet the needs of the Superfund program. The procedures are intended for use by EPA remedial project managers, enforcement project managers, and air experts as well as by EPA Superfund contractors. The emphasis of this volume is to provide a recommended APA procedure relative to the remedial phase of the Superfund process.

Environmental Protection Agency (EPA). 1989g. Air Superfund National Technical Guidance Series. Volume II: Estimation of Baseline Air Emissions at Superfund Sites. Interim Final. Office of Air Quality Planning and Standards. Research Triangle Park, NC. EPA/450/1-89/002.

- This volume provides information concerning procedures for developing baseline emissions from landfills and lagoons. Describes baseline emissions from both undisturbed sites and sites where media-disturbing activities are taking place. The procedures described for landfills may be applied to solid hazardous waste, and those for lagoons may be applied to liquid hazardous waste.

Environmental Protection Agency (EPA). 1989h. Air Superfund National Technical Guidance Series. Volume III: Estimation of Air Emissions from Cleanup Activities at Superfund Sites. Interim Final. Office of Air Quality Planning and Standards. Research Triangle Park, NC. EPA/450/1-89/003.

- This volume provides technical guidance for estimating air emissions from remedial activities at NPL sites that may impact local air quality for both onsite workers at a site and the surrounding community while the remedial activities are occurring. Discusses methods to characterize air quality impacts during soil removal, incineration, and air stripping.

Environmental Protection Agency (EPA). 1989i. Guidance Manual for Assessing Human Health Risks from Chemically Contaminated Fish and Shellfish. Office of Marine and Estuarine Protection. EPA/503/8-89/002.

- Study designed to measure concentrations of toxic substances in edible tissues of fish and shellfish.

Environmental Protection Agency (EPA) and Army Corps of Engineers (COE). 1981. Procedures for Handling and Chemical Analysis of Sediment and Water Samples. Technical Committee on Dredged and Fill Material. Technical Report EPA/DE-81-1.

Food and Drug Administration (FDA). 1977. Pesticide Analytical Manual. Volume I.

- Provides a skin-on fillet (whole fish sampling) protocol used in USEPA monitoring of sportfish in the Great Lakes. Also includes information on compositing.

Food and Drug Administration (FDA). 1986. Pesticides and Industrial Chemicals in Domestic Foods.

- Provides guidance for sampling designs for fishery products from the market.

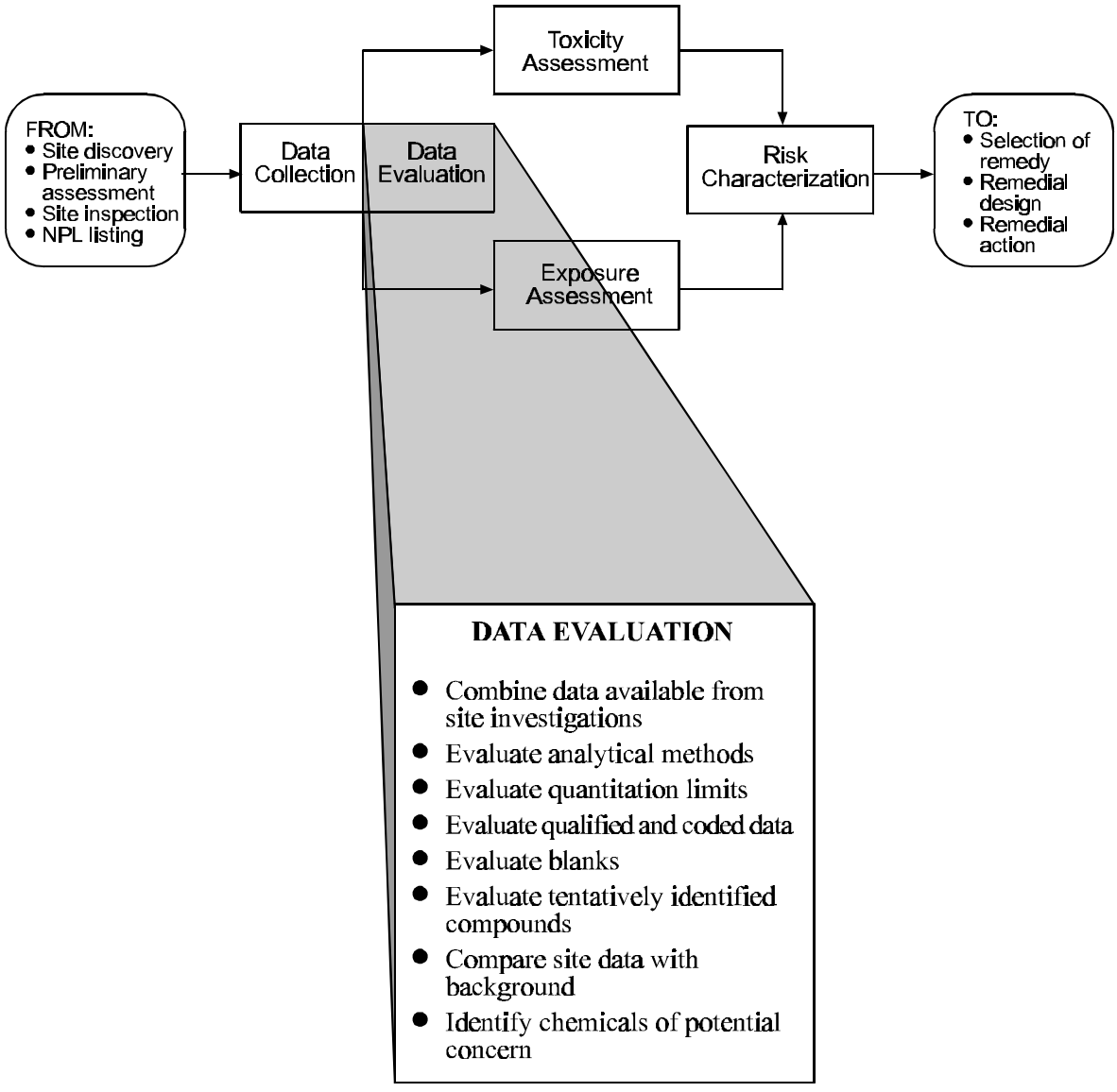
Freeman, H.M. 1989. Standard Handbook of Hazardous Waste Treatment and Disposal. McGraw-Hill. New York.

- Provides detailed information concerning sampling and monitoring of hazardous wastes at remedial action sites (Chapters 12 and 13).

Gilbert, R.O. 1987. Statistical Methods for Environmental Pollution Monitoring. Van Nostrand Reinhold. New York.

- Provides statistical analysis information by providing sampling plans, statistical tests, parameter estimation procedure techniques, and references to pertinent publications. The statistical techniques discussed are relatively simple, and examples, exercise, and case studies are provided to illustrate procedures.

CHAPTER 5
DATA EVALUATION



CHAPTER 5

DATA EVALUATION

After a site sampling investigation has been completed (see Chapter 4), a large quantity of analytical data is usually available. Each sample may have been analyzed for the presence of over one hundred chemicals, and many of those chemicals may have been detected. The following nine steps should be followed to organize the data into a form appropriate for a baseline risk assessment:

(1) gather all data available from the site investigation and sort by medium (Section 5.1);

(2) evaluate the analytical methods used (Section 5.2);

(3) evaluate the quality of data with respect to sample quantitation limits (Section 5.3);

(4) evaluate the quality of data with respect to qualifiers and codes (Section 5.4);

(5) evaluate the quality of data with respect to blanks (Section 5.5);

(6) evaluate tentatively identified compounds (Section 5.6);

(7) compare potential site-related contamination with background (Section 5.7);

(8) develop a set of data for use in the risk assessment (Section 5.8); and

(9) if appropriate, further limit the number of chemicals to be carried through the risk assessment (Section 5.9).

Prior to conducting any of these steps, the EPA remedial project manager (RPM) should be consulted to determine if certain steps should be modified, added, or deleted as a result of site-specific conditions. Also, some of the steps may be conducted outside the context of the risk assessment (e.g., for the feasibility study). The rationale for not evaluating certain data based on any of these steps must be fully discussed in the text of the risk assessment report.

The following sections address each of the data evaluation steps in detail, and Exhibit 5-1 presents a flowchart of the process. The outcome of this evaluation is (1) the identification of a set of chemicals that are likely to be site-related and (2) reported concentrations that are of acceptable quality for use in the quantitative risk assessment.

ACRONYMS FOR CHAPTER 5

CLP = Contract Laboratory Program
CRDL = Contract-Required Detection Limit
CRQL = Contract-Required Quantitation Limit
DL = Detection Limit
FIT = Field Investigation Team
IDL = Instrument Detection Limit
MDL = Method Detection Limit
ND = Non-detect
PE = Performance Evaluation
PQL = Practical Quantitation Limit
QA/QC = Quality Assurance/Quality Control
QL = Quantitation Limit
RAS = Routine Analytical Services
SAS = Special Analytical Services
SMO = Sample Management Office
SOW = Statement of Work
SQL = Sample Quantitation Limit
SVOC = Semivolatile Organic Chemical
TCL = Target Compound List
TIC = Tentatively Identified Compound
TOC = Total Organic Carbon
TOX = Total Organic Halogens
VOC = Volatile Organic Chemical

DEFINITIONS FOR CHAPTER 5

Chemicals of Potential Concern. Chemicals that are potentially site-related and whose data are of sufficient quality for use in the quantitative risk assessment.

Common Laboratory Contaminants. Certain organic chemicals (considered by EPA to be acetone, 2-butanone, methylene chloride, toluene, and the phthalate esters) that are commonly used in the laboratory and thus may be introduced into a sample from laboratory cross-contamination, not from the site.

Contract-required Quantitation Limit (CRQL). Chemical-specific levels that a CLP laboratory must be able to routinely and reliably detect and quantitate in specified sample matrices. May or may not be equal to the reported quantitation limit of a given chemical in a given sample.

Detection Limit (DL). The lowest amount that can be distinguished from the normal "noise" of an analytical instrument or method.

Non-detects (NDs). Chemicals that are not detected in a particular sample above a certain limit, usually the quantitation limit for the chemical in that sample. Non-detects may be indicated by a "U" data qualifier.

Positive Data. Analytical results for which measurable concentrations (i.e., above a quantitation limit) are reported. May have data qualifiers attached (except a U, which indicates a non-detect).

Quantitation Limit (QL). The lowest level at which a chemical can be accurately and reproducibly quantitated. Usually equal to the instrument detection limit multiplied by a factor of three to five, but varies for different chemicals and different samples.

If the nine data evaluation steps are followed, the number of chemicals to be considered in the remainder of the risk assessment usually will be less than the number of chemicals initially identified. Chemicals remaining in the quantitative risk assessment based upon this evaluation are referred to in this guidance as "chemicals of potential concern."

5.1 COMBINING DATA AVAILABLE FROM SITE INVESTIGATIONS

Gather data, which may be from several different sampling periods and based on several different analytical methods, from all available sources, including field investigation team (FIT) reports, remedial investigations, preliminary site assessments, and ongoing site characterization and alternatives screening activities. Sort data by medium. A useful table format for presenting data is shown in Exhibit 5-2.

Evaluate data from different time periods to determine if concentrations are similar or if changes have occurred between sampling periods. If the methods used to analyze samples from different time periods are similar in terms of the types of analyses conducted and the QA/QC procedures followed, and if the concentrations between sampling periods are similar, then the data may be combined for the purposes of quantitative risk assessment in order to obtain more information to characterize the site. If concentrations of chemicals change significantly between sampling periods, it may be useful to keep the data separate and evaluate risks separately. Alternatively, one could use only the most recent data in the quantitative risk assessment and evaluate older data in a qualitative analysis of changes in concentrations over time. The RPM should be consulted on the elimination of any data sets from the risk assessment, and justification for such elimination must be fully described in the risk assessment report.

EXHIBIT 5-1
DATA EVALUATION

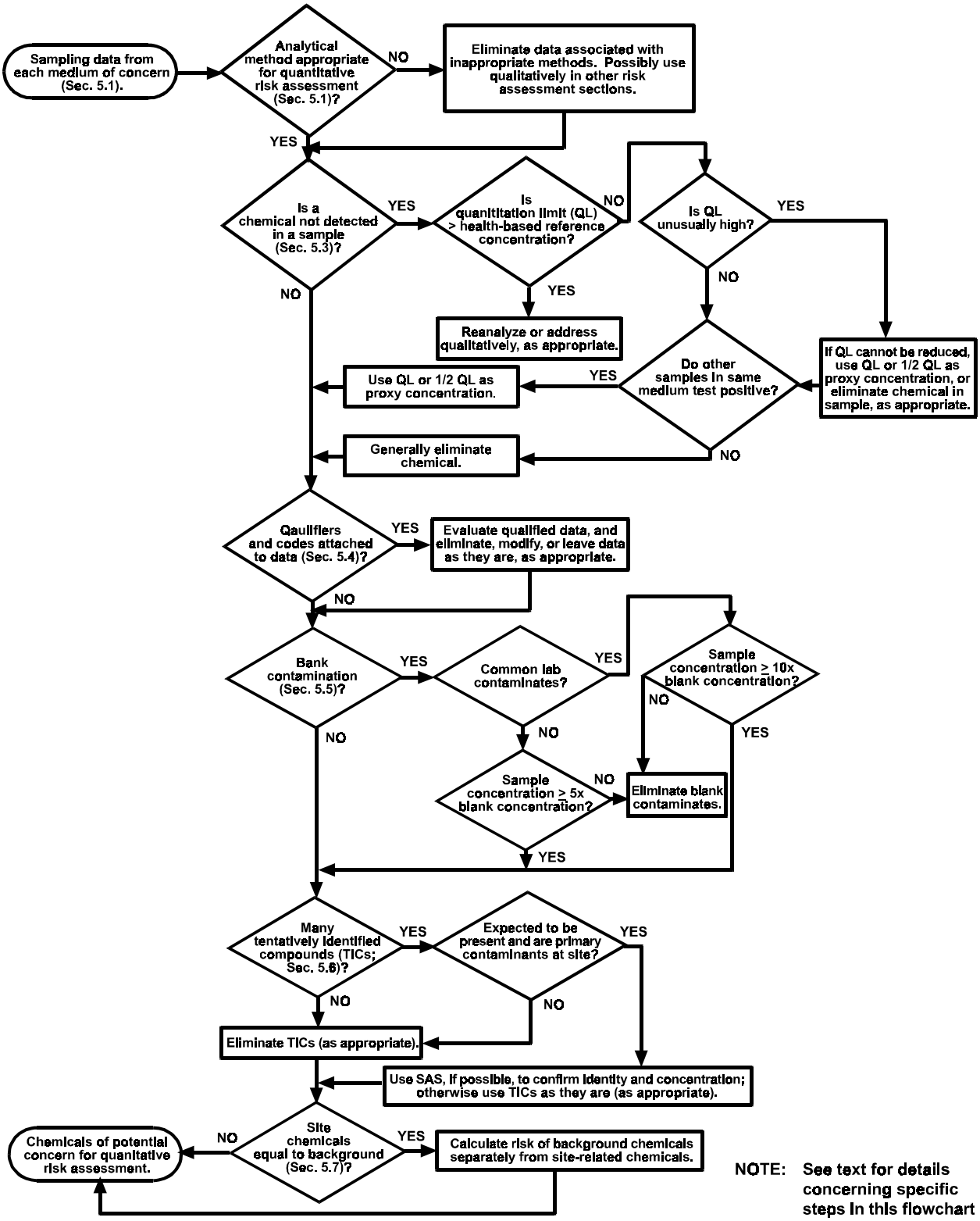


EXHIBIT 5-2

EXAMPLE OF OUTPUT FORMAT FOR VALIDATED DATA

	Area X		
Sample Medium	Soil	Soil	Soil
Sample ID	SRB-3-1	SRB-3-1DU	SRB-3-2
Sample or Screen Depth	0-1'	0-1'	2-4'
Date Collected	12/14/87	12/14/87	12/10/87
Units	ug/kg	ug/kg	ug/kg
Blanks or Duplicates		Duplicate	

Chemical	CRQL[a]	Concentration	Qualifier[b]	CRQL[a]	Concentration	Qualifier[b]	CRQL[a]	Concentration	Qualifier[b]
Aroclor-1016	80	80	U	80	80	U	2000[c]	2000	UJ
Aroclor-1221	80	80	U	80	80	U	2000[c]	2000	UJ
Aroclor-1232	80	80	U	80	80	U	2000[c]	2000	UJ
Aroclor-1242	80	40	J	80	42	J	2000[c]	2000	UJ
Aroclor-1248	80	30	J	80	36	J	2000[c]	2000	UJ
Aroclor-1254	160	120	J	160	110	J	2000[c]	1800	J
Aroclor-1260	160	210		160	220		2000[c]	2100	

Note: All values other than qualifiers must be entered as numbers, not as labels.

[a] Contract-required quantitation limit (unless otherwise noted). Values for illustration only.

[b] Refer to Section 5.4 for an explanation of qualifiers.

[c] Sample quantitation limit.

5.2 EVALUATION OF ANALYTICAL METHODS

Group data according to the types of analyses conducted (e.g., field screening analysis, semivolatiles analyzed by EPA methods for water and wastewater, semivolatiles analyzed by EPA's Superfund Contract Laboratory Program [CLP] procedures) to determine which analytical method results are appropriate for use in quantitative risk assessment. Often, this determination has been made already by regional and contractor staff.

An overview of EPA analytical methods is provided in the box below. Exhibit 5-3 presents examples of the types of data that are not usually appropriate for use in quantitative risk assessment, even though they may be available from a site investigation.

OVERVIEW OF THE CLP AND OTHER EPA ANALYTICAL METHODS

The EPA Contract Laboratory Program (CLP) is intended to provide analytical services for Superfund waste site samples. As discussed in the *User's Guide to the Contract Laboratory Program* (EPA 1988a, hereafter referred to as the CLP User's Guide), the program was developed to fill the need for legally defensible results supported by a high level of quality assurance (i.e., data of known quality) and documentation.

Prior to becoming CLP laboratories, analytical laboratories must meet stringent requirements for laboratory space and practices, instrumentation, personnel training, and quality control (QC), and also must successfully analyze performance evaluation (PE) samples. Before the first samples are shipped to the laboratory, audits of CLP labs are conducted to verify all representations made by laboratory management. Continuing performance is monitored by periodic PE sample analyses, routine and remedial audits, contract compliance screening of data packages, and oversight by EPA.

Superfund samples are most commonly analyzed using the Routine Analytical Services (RAS) conducted by CLP laboratories. Under RAS, all data are generated using the same analytical protocols specifying instrumentation, sample handling, analysis parameters, required quantitation limits, QC requirements, and report format. Protocols are provided in the *CLP Statement of Work (SOW) for Inorganics* (EPA 1988b) and the *CLP Statement of Work for Organics* (1988c). The SOWs also contain EPA's target analyte or compound lists (TAL for inorganics, TCL for organics), which are the lists of analytes and required quantitation limits (QLs) for which every Superfund site sample is routinely analyzed under RAS. As of June 1989, analytes on the TCL/TAL consist of 34 volatile organic chemicals (VOCs), 65 semivolatile organic chemicals (SVOCs), 19 pesticides, 7 polychlorinated biphenyls, 23 metals, and total cyanide. Finally, the SOW specifies data qualifiers that may be placed on certain data by the laboratory to communicate information and/or QC problems.

CLP labs are required to submit RAS data packages to EPA's Sample Management Office (SMO) and to the EPA region from which the samples originated within 35 days of receipt of samples. SMO provides management, operational, and administrative support to the CLP to facilitate optimal use of the program. SMO personnel identify incomplete or missing elements and verify compliance with QA/QC requirements in the appropriate SOW. In addition to the SMO review, all CLP data are inspected by EPA-appointed regional data validators. Using Laboratory Data Validation Functional Guidelines issued by EPA headquarters (hereafter referred to as Functional Guidelines for Inorganics [EPA 1988d] and Functional Guidelines for Organics [EPA 1988e]), regional guidelines, and professional judgment, the person validating data identifies deviations from the SOW, poor QC results, matrix interferences, and other analytical problems that may compromise the potential uses of the data. In the validation process, data may be flagged with qualifiers to alert data users of deviations from QC requirements. These qualifiers differ from those qualifiers attached to the data by the laboratory.

In addition to RAS, non-standard analyses may be conducted using Special Analytical Services (SAS) to meet user requirements such as short turnaround time, lower QLs, non-standard matrices, and the testing of analytes other than those on the Target Compound List. Under SAS, the user requests specific analyses, QC procedures, report formats, and timeframe needed.

Examples of other EPA analytical methods include those described in *Test Methods for Evaluating Solid Waste* (EPA 1986; hereafter referred to as SW-846 Methods) and *Methods for Organic Chemical Analysis of Municipal and Industrial Wastewater* (EPA 1984; hereafter referred to as EPA 600 Methods). The SW-846 Methods provide analytical procedures to test solid waste to determine if it is a hazardous waste as defined under the Resource Conservation and Recovery Act (RCRA). These methods include procedures for collecting solid waste samples and for determining reactivity, corrosivity, ignitability, composition of waste, and mobility of waste components. The EPA 600 Methods are used in regulatory programs under the Clean Water Act to determine chemicals present in municipal and industrial wastewaters.

EXHIBIT 5-3

EXAMPLES OF THE TYPES OF DATA POTENTIALLY UNSUITABLE FOR A QUANTITATIVE RISK ASSESSMENT

Analytical Instrument or Method	Purpose of Analysis	Analytical Result
HNu Organic Vapor Detector	Health and Safety, Field Screen	Total Organic Vapor
Organic Vapor Analyzer	Health and Safety, Field Screen	Total Organic Vapor
Combustible Gas Indicator	Health and Safety	Combustible Vapors, Oxygen-deficient Atmosphere
Field Gas Chromatography[a]	Field Screen/Analytical Method	Specific Volatile and Semi-volatile Organic Chemicals

[a] Depending on the detector used, this instrument can be sufficiently sensitive to yield adequate data for use in quantitative risk assessment; however, a confirming analysis by GC/MS should be performed on a subset of the samples in a laboratory prior to use.

Analytical results that are not specific for a particular compound (e.g., total organic carbon [TOC], total organic halogens [TOX]) or results of insensitive analytical methods (e.g., analyses using portable field instruments such as organic vapor analyzers and other field screening methods) may be useful when considering sources of contamination or potential fate and transport of contaminants. These types of analytical results, however, generally are not appropriate for quantitative risk assessment; therefore, the risk assessor may not want to include them in the summary of chemicals of potential concern for the quantitative risk assessment. In addition, the results of analytical methods associated with unknown, few, or no QA/QC procedures should be eliminated from further quantitative use. These types of results, however, may be useful for qualitative discussions of risk in other sections of the risk assessment report.

The outcome of this step is a set of site data that has been developed according to a standard set of sensitive, chemical-specific methods (e.g., SW-846 Methods [EPA 1986], EPA 600 Methods [EPA 1984], CLP Statements of Work [EPA 1988b,c]), with QA/QC procedures that are well-documented and traceable. The data resulting from analyses conducted under the CLP, which generally comprise the majority of results available from a Superfund site investigation, fall into this category.

Although the CLP was developed to ensure that consistent QA/QC methods are used when analyzing Superfund site samples, it does not ensure that all analytical results are consistently of sufficient quality and reliability for use in quantitative risk assessment. Neither the CLP nor QA/QC procedures associated with other methods make judgments concerning the ultimate "usability" of the data. Do not accept at face value all remaining analytical results, whether from the CLP or from some other set of analytical methodologies. Instead, determine -- according to the steps discussed below -- the limitations and uncertainties associated with the data so that only data that are appropriate and reliable for use in a quantitative risk assessment are carried through the process.

5.3 EVALUATION OF QUANTITATION LIMITS

This step involves evaluation of quantitation limits and detection limits (QLs and DLs) for all of the chemicals assessed at the site. This evaluation may lead to the re-analysis of some samples, the use of "proxy" (or estimated) concentrations, and/or the elimination of certain chemicals from further consideration (because they are believed to be absent from the site). Types and definitions of QLs and DLs are presented in the box on the next page.

Before eliminating chemicals because they are not detected (or conducting any other manipulation of the data), the following points should be considered:

(1) the sample quantitation limit (SQL) of a chemical may be greater than corresponding standards, criteria, or concentrations derived from toxicity reference values (and, therefore, the chemical may be present at levels greater than these corresponding reference concentrations, which may result in undetected risk); and

(2) a particular SQL may be significantly higher than positively detected values in other samples in a data set.

These two points are discussed in detail in the following two subsections. A third subsection provides guidance for situations where only some of the samples for a given medium test positive for a particular chemical. A fourth subsection addresses the special situation where SQLs are not available. The final subsection addresses the specific steps involved with elimination of chemicals from the quantitative risk assessment based on their QLs.

5.3.1 SAMPLE QUANTITATION LIMITS (SQLs) THAT ARE GREATER THAN REFERENCE CONCENTRATIONS

As discussed in Chapter 4, QLs needed for the site investigation should be specified in the sampling plan. For some chemicals, however,

SQLs obtained under RAS or SAS may exceed certain reference concentrations (e.g., maximum contaminant levels [MCLs], concentrations corresponding to a 10^{-6} cancer risk). The box on the next page illustrates this problem. For certain chemicals (e.g., antimony), the CLP contract-required quantitation limits (CRQLs) exceed the corresponding reference concentrations for noncarcinogenic effects, based on the EPA-verified reference dose and a 2-liter per day ingestion of water by a 70-kilogram person.[1] Estimation of cancer risks for several other chemicals (e.g., arsenic, styrene) at their CRQLs yields cancer risks exceeding 10^{-4}, based on the same water ingestion factors. Most potential carcinogens with EPA-derived slope factors have CRQLs that yield cancer risk levels exceeding 10^{-6} in water, and none of the carcinogens with EPA-derived slope factors have CRQL values yielding less than 10^{-7} cancer risk levels (as of the publication date of this manual; data not shown).

Three points should be noted when considering this example.

(1) Review of site information and a preliminary determination of chemicals of potential concern at a site prior to sample collection may allow the specification of lower QLs (i.e., using SAS) before an investigation begins (see Chapter 4). This is the most efficient way to minimize the problem of QLs exceeding levels of potential concern.

(2) EPA's Analytical Operations Branch currently is working to reduce the CRQL values for several chemicals on the TCL and TAL, and to develop an analytical service for chemicals with special standards (e.g., MCLs).

TYPES AND DEFINITIONS OF DETECTION LIMITS AND QUANTITATION LIMITS

Strictly interpreted, the detection limit (DL) is the lowest amount of a chemical that can be "seen" above the normal, random noise of an analytical instrument or method. A chemical present below that level cannot reliably be distinguished from noise. DLs are chemical-specific and instrument-specific and are determined by statistical treatment of multiple analyses in which the ratio of the lowest amount observed to the electronic noise level (i.e., the signal-to-noise ratio) is determined. On any given day in any given sample, the calculated limit may not be attainable; however, a properly calculated limit can be used as an overall general measure of laboratory performance.

Two types of DLs may be described -- instrument DLs (IDLs) and method DLs (MDLs). The IDL is generally the lowest amount of a substance that can be detected by an instrument; it is a measure only of the DL for the instrument, and does not consider any effects that sample matrix, handling, and preparation may have. The MDL, on the other hand, takes into account the reagents, sample matrix, and preparation steps applied to a sample in specific analytical methods.

Due to the irregular nature of instrument or method noise, reproducible quantitation of a chemical is not possible at the DL. Generally, a factor of three to five is applied to the DL to obtain a quantitation limit (QL), which is considered to be the lowest level at which a chemical may be accurately and reproducibly quantitated. DLs indicate the level at which a small amount would be "seen," whereas QLs indicate the levels at which measurements can be "trusted."

Two types of QLs may be described -- contract-required QLs (CRQLs) and sample QLs (SQLs). (Contract-required detection limits [CRDL] is the term used for inorganic chemicals. For the purposes of this manual, however, CRQL will refer to both organic and inorganic chemicals.) In order to participate in the CLP, a laboratory must be able to meet EPA CRQLs. CRQLs are chemical-specific and vary depending on the medium analyzed and the amount of chemical expected to be present in the sample. As the name implies, CRQLs are not necessarily the lowest detectable levels achievable, but rather are levels that a CLP laboratory should routinely and reliably detect and quantitate in a variety of sample matrices. A specific sample may require adjustments to the preparation or analytical method (e.g., dilution, use of a smaller sample aliquot) in order to be analyzed. In these cases, the reported QL must in turn be adjusted. Therefore, SQLs, not CRQLs, will be the QLs of interest for most samples. In fact, for the same chemical, a specific SQL may be higher than, lower than, or equal to SQL values for other samples. In addition, preparation or analytical adjustments such as dilution of a sample for quantitation of an extremely high level of only one compound could result in non-detects for all other compounds included as analytes for a particular method, even though these compounds may have been present at trace quantities in the undiluted sample. Because SQLs take into account sample characteristics, sample preparation, and analytical adjustments, these values are the most relevant QLs for evaluating non-detected chemicals.

EXAMPLE OF HEALTH RISKS FROM INGESTION OF WATER CONTAMINATED WITH SELECTED CHEMICALS AT THEIR QUANTITATION LIMITS[a]

Chemical	CAS #	CRQL or CRDL (ug/L)[b]	Cancer Risk CRDL/RfC[c]	at CRQL or CRDL[d]
Antimony	7440-36-0	60	4.3	
Arsenic	7440-38-2	10	$5x10^{-4}$	
Benz(a)pyrene	50-32-8	10		$3x10^{-3}$
Bis(2-Chloroethyl)ether	111-44-4	10		$3x10^{-4}$
2,4-Dinitrotoluene	121-14-2	10		$2x10^{-4}$
Hexachlorobenzene	118-74-1	10		$5x10^{-4}$
N-Nitroso-di-n-dipropylamine	621-64-7	10		$2x10^{-3}$
PCB-1254	11096-69-1	1	$2x10^{-4}$[e]	
PCB-1260	11096-82-5	1	$2x10^{-4}$	
Styrene	100-42-5	5	$4x10^{-4}$	
Vinyl chloride	75-01-4	10		$7x10^{-4}$

[a] All values in this example are for illustration purposes only.

[b] CRQL = Contract-required quantitation limit (organics) of the Contract Laboratory Program (revised April 1989).
CRDL = Contract-required detection limit (inorganics) of the Contract Laboratory Program (revised July 1988).

The CRQL and CRDL values presented here are for the regular multi-media multi-concentration CLP methods.

[c] RfC = Reference concentration (based on the August 1989 reference dose for oral exposure, assuming a 70-kilogram adult drinks 2 liters of contaminated water per day).

[d] Cancer Risk at CRQL or CRDL = Excess upper-bound lifetime cancer risk (based on the August 1989 slope factor for oral exposure, assuming a 70-kilogram adult drinks 2 liters of contaminated water per day).

[e] PCB-1260 slope factor was used.

(3) In several situations, an analytical laboratory may be able to attain QLs in particular samples that are below or above the CRQL values.

If SAS was not specified before sampling began and/or if a chemical is not detected in any sample from a particular medium at the QL, then available modeling data, as well as professional judgment, should be used to evaluate whether the chemical may be present above reference concentrations. If the available information indicates the chemical is not present, see Section 5.3.5 for guidance on eliminating chemicals. If there is some indication that the chemical is present, then either re-analyze selected samples using SAS, if time allows, or address the chemical qualitatively. In determining which option is most appropriate for a site, a screening-level risk assessment should be performed by assuming that the chemical is present in the sample at the SQL (see Section 5.3.4 for situations where SQLs are not available). Carry the chemical through the screening risk assessment, essentially conducting the assessment on the SQL for the particular chemical. In this way, the risks that would be posed if the chemical is present at the SQL can be compared with risks posed by other chemicals at the site.

Re-analyze the sample. This (preferred) option discourages elimination of questionable chemicals (i.e., chemicals that may be present below their QL but above a level of potential concern) from the risk assessment. If time allows and a sufficient quantity of the sample is available, submit a SAS request to re-analyze the sample at QLs that are below reference concentrations. The possible outcome of

this option is inclusion of chemicals positively detected at levels above reference concentrations but below the QLs that would normally have been attained under routine analysis of Superfund samples in the CLP program.

Address the chemical qualitatively. A second and less desirable option for a chemical that may be present below its QL (and possibly above its health-based reference concentration) is to eliminate the chemical from the quantitative risk assessment, noting that if the chemical was detected at a lower QL, then its presence and concentration could contribute significantly to the estimated risks.

5.3.2 UNUSUALLY HIGH SQLs

Due to one or more sample-specific problems (e.g., matrix interferences), SQLs for a particular chemical in some samples may be unusually high, sometimes greatly exceeding the positive results reported for the same chemical in other samples from the data set. Even if these SQLs do not exceed health-based standards or criteria, they may still present problems. If the SQLs cannot be reduced by re-analyzing the sample (e.g., through the use of SAS or sample cleaning procedures to remove matrix interferences), exclude the samples from the quantitative risk assessment if they cause the calculated exposure concentration (i.e., the concentration calculated according to guidance in Chapter 6) to exceed the maximum detected concentration for a particular sample set. The box on this page presents an example of how to address a situation with unusually high QLs.

EXAMPLE OF UNUSUALLY HIGH QUANTIFICATION LIMITS

In this example, concentrations of semivolatile organic chemicals in soils have been determined using the CLP's RAS.

	Concentration (ug/kg)			
Chemical	Sample 1	Sample 2	Sample 3	Sample 4
Phenol	330 U[a]	390	19,000 U	490

[a] U = Compound was analyzed for, but not detected. Value presented (e.g., 330 U) is the SQL.

The QLs presented in this example (i.e., 330 to 19,000 ug/kg) vary widely from sample to sample. SAS would not aid in reducing the unusually high QL of 19,000 ug/kg noted in Sample 3, assuming it was due to unavoidable matrix interferences. In this case, the result for phenol in Sample 3 would be eliminated from the quantitative risk assessment because it would cause the calculated exposure concentrations (from Chapter 6) to exceed the maximum detected concentration (in this case 490 ug/kg). Thus, the data set would be reduced to three samples: the non-detect in Sample 1 and the two detected values in Samples 2 and 4.

5.3.3 WHEN ONLY SOME SAMPLES IN A MEDIUM TEST POSITIVE FOR A CHEMICAL

Most analytes at a site are not positively detected in each sample collected and analyzed. Instead, for a particular chemical the data set generally will contain some samples with positive results and others with non-detected results. The non-detected results usually are reported as SQLs. These limits indicate that the chemical was not measured above certain levels, which may vary from sample to sample. The chemical may be present at a concentration just below the reported quantitation limit, or it may not be present in the sample at all (i.e., the concentration in the sample is zero).

In determining the concentrations most representative of potential exposures at the site (see Chapter 6), consider the positively detected results together with the non-detected results (i.e., the SQLs). If there is reason to believe that the chemical is present in a sample at a concentration below the SQL, use one-half of the SQL as a proxy concentration. The SQL value itself can be used if there is reason to believe the concentration is closer to it than to one-half the SQL. (See the next subsection for situations where SQLs are not available.) Unless site-specific information indicates that a chemical is not likely to be present in a sample, do not substitute the value zero in place of the SQL (i.e., do not assume that a chemical that is not detected at the SQL would not be detected in the sample if the analysis was extremely sensitive). Also, do not simply omit the non-detected results from the risk assessment.

5.3.4 WHEN SQLs ARE NOT AVAILABLE

A fourth situation concerning QLs may sometimes be encountered when evaluating site data. For some sites, data summaries may not provide the SQLs. Instead, MDLs, CRQLs, or even IDLs may have been substituted wherever a chemical was not detected. Sometimes, no detection or quantitation limits may be provided with the data. As a first step in these situations, always attempt to obtain the SQLs, because these are the most appropriate limits to consider when evaluating non-detected chemicals (i.e., they account for sample characteristics, sample preparation, or analytical adjustments that may differ from sample to sample).

If SQLs cannot be obtained, then, for CLP sample analyses, the CRQL should be used as the QL of interest for each non-detected chemical, with the understanding that these limits may overestimate or underestimate the actual SQL. For samples analyzed by methods different from CLP methods, the MDL may be used as the QL, with the understanding that in most cases this will underestimate the SQL (because the MDL is a measure of detection limits only and does not account for sample characteristics or matrix interferences). Note that the IDL should rarely be used for non-detected chemicals since it is a measure only of the detection limit for a particular instrument and does not consider the effect of sample handling and preparation or sample characteristics.

5.3.5 WHEN CHEMICALS ARE NOT DETECTED IN ANY SAMPLES IN A MEDIUM

After considering the discussion provided in the above subsections, generally eliminate those chemicals that have not been detected in any samples of a particular medium. On CLP data reports, these chemicals will be designated in each sample with a U qualifier preceded by the SQL or CRQL (e.g., 10 U). If information exists to indicate that the chemicals are present, they should not be eliminated. For example, if chemicals with similar transport and fate characteristics are detected frequently in soil at a site, and some of these chemicals also are detected frequently in ground water while the others are not detected, then the undetected chemicals are probably present in the ground water and therefore may need to be included in the risk assessment as ground-water contaminants.

The outcome of this step is a data set that only contains chemicals for which positive data (i.e., analytical results for which measurable concentrations are reported) are available in at least one sample from each medium. Unless otherwise indicated, assume at this point in the evaluation of data that positive data to which no uncertainties are attached concerning either the assigned identity of the chemical or the reported concentration (i.e., data that are not "tentative," "uncertain," or "qualitative") are appropriate for use in the quantitative risk assessment.

5.4 EVALUATION OF QUALIFIED AND CODED DATA

For CLP analytical results, various qualifiers and codes (hereafter referred to as qualifiers) are attached to certain data by either the laboratories conducting the analyses or by persons performing data validation. These qualifiers often pertain to QA/QC problems and generally indicate questions concerning chemical identity, chemical concentration, or both. All qualifiers must be addressed before the chemical can be used in quantitative risk assessment. Qualifiers used by the laboratory may differ from those used by data validation personnel in either identity or meaning.

5.4.1 TYPES OF QUALIFIERS

A list of the qualifiers that laboratories are permitted to use under the CLP -- and their potential use in risk assessment -- is presented in Exhibit 5-4. A similar list addressing data validation qualifiers is provided in Exhibit 5-5. In general, because the data validation process is intended to assess the effect of QC issues on data usability, validation data qualifiers are attached to the data after the laboratory qualifiers and supersede the laboratory qualifiers. If data have both laboratory and validation qualifiers and they appear contradictory, ignore the laboratory qualifier and consider only the validation qualifier. If qualifiers have been attached to certain data by the laboratory and have not been removed, revised, or superseded during data validation, then evaluate the

EXHIBIT 5-4

CLP LABORATORY DATA QUALIFIERS AND THEIR POTENTIAL USE IN QUANTITATIVE RISK ASSESSMENT

Qualifier	Definition	Indicates: Uncertain Identity?	Uncertain Concentration?	Include Data in Quantitative Risk Assessment?
Inorganic Chemical Data:[a]				
B	Reported value is <CRDL, but >IDL.	No	No	Yes
U	Compound was analyzed for, but not detected.	Yes	Yes	?
E	Value is estimated due to matrix interferences.	No	Yes	Yes
M	Duplicate injection precision criteria not met.	No	Yes	Yes
N	Spiked sample recovery not within control limits.	No	Yes	Yes
S	Reported value was determined by the Method of Standard Additions (MSA).	No	No	Yes
W	Post-digestion spike for furnace AA analysis is out of control limits, while sample absorbance is <50% of spike absorbance.	No	Yes	Yes
*	Duplicate analysis was not within control limits.	No	Yes	Yes
+	Correlation coefficient for MSA was <0.995.	No	Yes	Yes
Organic Chemical Data:[b]				
U	Compound was analyzed for, but not detected.	Yes	Yes	?but not

(continued)

EXHIBIT 5-4 (continued)

CLP LABORATORY DATA QUALIFIERS AND THEIR POTENTIAL USE IN QUANTITATIVE RISK ASSESSMENT

Qualifier	Definition	Indicates: Uncertain Identity?	Uncertain Concentration?	Include Data in Quantitative Risk Assessment?
J	Value is estimated, either for a tentatively identified compound (TIC) or when a compound is present (spectral identification criteria are met, but the value is <CRQL).	No, for TCL chemicals; Yes, for TICs	Yes	?
C	Pesticide results were confirmed by GC/MS.	No	No	Yes
B	Analyte found in associated blank as well as in sample.[c]	No	Yes	Yes
E	Concentration exceeds calibration range of GC/MS instrument.	No	Yes	Yes
D	Compound identified in an analysis at a secondary dilution factor.	No	No	Yes
A	The TIC is a suspected aldol-condensation product.	Yes	Yes	No
X	Additional flags defined separately.	--	--	--

-- = Data will vary with laboratory conducting analyses.

[a] Source: EPA 1988b.

[b] Source: EPA 1988c.[c] See Section 5.5 for guidance concerning blank contamination.

EXHIBIT 5-5

VALIDATION DATA QUALIFIERS AND THEIR POTENTIAL USE IN QUANTITATIVE RISK ASSESSMENT

Qualifier	Definition	Indicates: Uncertain Identity?	Uncertain Concentration?	Include Data in Quantitative Risk Assessment?
Inorganic and Organic Chemical Data:[a]				
U	The material was analyzed for, but not detected. The associated numerical value is the SQL.	Yes	Yes	?
J	The associated numerical value is an estimated quantity.	No	Yes	Yes
R	Quality control indicates that the data are unusable (compound may or may not be present). Re-sampling and/or re-analysis is necessary for verification.	Yes	Yes	No
Z	No analytical result (inorganic data only).	--	--	--
Q	No analytical result (organic data only).	--	--	--
N	Presumptive evidence of presence of material (tentative identification).[b]	Yes	Yes	?

-- = Not applicable

[a] Source: EPA 1988d,e.

[b] Organic chemical data only.

laboratory qualifier itself. If it is unclear whether the data have been validated, contact the appropriate data validation and/or laboratory personnel.

The type of qualifier and other site-specific factors determine how qualified data are to be used in a risk assessment. As seen in Exhibits 5-4 and 5-5, the type of qualifier attached to certain data often indicates how that data should be used in a risk assessment. For example, most of the laboratory qualifiers for both inorganic chemical data and organic chemical data (e.g., J, E, N) indicate uncertainty in the reported concentration of the chemical, but not in its assigned identity. Therefore, these data can be used just as positive data with no qualifiers or codes. In general, include data with qualifiers that indicate uncertainties in concentrations but not in identification.

Examples showing the use of certain qualified data are presented in the next two boxes. The first box addresses the J qualifier, the most commonly encountered data qualifier in Superfund data packages. Basically, the guidance here is to use J-qualified concentrations the same way as positive data that do not have this qualifier. If possible, note potential uncertainties associated with the qualifier, so that if data qualified with a J contribute significantly to the risk, then appropriate caveats can be attached.

EXAMPLE OF J QUALIFIERS

In this example, concentrations of volatile organic chemicals in ground water have been determined using the CLP's RAS.

	Concentration (ug/L)			
Chemical	Sample 1	Sample 2	Sample 3	Sample 4
Tetrachloro-ethene	14,000 J[a]	40	30 U[b]	20 J

[a] J = The numerical value is an estimated quantity.
[b] U = Compound was analyzed for, but not detected. Value presented (e.g., 30 U) is the SQL.

Tetrachlorethene was detected in three of four samples at concentrations of 14,000 µg/1, 40 µg/1, and 20 ug/1; therefore, these concentrations -- as well as the non-detect -- should be used in determining representative concentrations.

An illustration of the use of R-qualified data is presented in the box in this column. The definition, and therefore the use of the R qualifier, differs depending on whether the data have been validated or not. (Note that the CLP formerly used R as a laboratory qualifier to indicate low spike recovery for inorganics. This has been changed, but older data may still have been qualified by the laboratory with an R.) If it is known that the R data qualifier indicates that the sample result was rejected by the data validation personnel, then this result should be eliminated from the risk assessment; if the R data qualifier was placed on the data to indicate estimated data due to low spike recovery (i.e., the R was placed on the data by the laboratory and not by the validator), then use the R-qualified data in a manner similar to the use of J-qualified data (i.e., use the R-qualified concentrations the same way as positive data that do not have this qualifier). If possible, note whether the R-qualified data are overestimates or underestimates of actual expected chemical concentrations so that appropriate caveats may be attached if data qualified with an R contribute significantly to the risk.

EXAMPLE OF VALIDATED DATA CONTAINING R QUALIFIERS

In this example, concentrations of inorganic chemicals in ground water have been determined using the CLP's RAS.

	Concentration (ug/L)			
Chemical	Sample 1	Sample 2	Sample 3	Sample 4
Manganese	310	500 R[a]	30 UR[b]	500

[a] R = Quality control indicates that the data are unusable (compound may or may not be present).

[b] U = Compound was analyzed for, but not detected. Value presented (e.g., 30 U) is the SQL.

These data have been validated, and therefore the R qualifiers indicate that the person conducting the data validation rejected the data for manganese in Samples 2 and 3. The "UR" qualifier means that manganese was not detected in Sample 3; however, the data validator rejected the non-detected result. Eliminate these two samples so that the data set now consists of only two samples (Samples 1

5.4.2 USING THE APPROPRIATE QUALIFIERS

The information presented in Exhibits 5-4 and 5-5 is based on the most recent EPA guidance documents concerning qualifiers: the SOW for Inorganics and the SOW for Organics (EPA 1988b,c) for laboratory qualifiers, and the Functional Guidelines for Inorganics and the Functional Guidelines for Organics (EPA 1988d,e) for validation qualifiers. The types and definitions of qualifiers, however, may be periodically updated within the CLP program. In addition, certain EPA regions may have their own data qualifiers and associated definitions. These regional qualifiers are generally consistent with the Functional Guidelines, but are designed to convey additional information to data users.

In general, the risk assessor should check whether the information presented in this section is current by contacting the appropriate regional CLP or headquarters Analytical Operations Branch staff. Also, if definitions are not reported with the data, regional contacts should be consulted prior to evaluating qualified data. These variations may affect how data with certain qualifiers should be used in a risk assessment. Make sure that definitions of data qualifiers used in the data set for the site have been reported with the data and are current. Never guess about the definition of qualifiers.

5.5 COMPARISON OF CONCENTRATIONS DETECTED IN BLANKS WITH CONCENTRATIONS DETECTED IN SAMPLES

Blank samples provide a measure of contamination that has been introduced into a sample set either (1) in the field while the samples were being collected or transported to the laboratory or (2) in the laboratory during sample preparation or analysis. To prevent the inclusion of non-site-related contaminants in the risk assessment, the concentrations of chemicals detected in blanks must be compared with concentrations of the same chemicals detected in site samples. Detailed definitions of different types of blanks are provided in the box on the next page.

Blank data should be compared with results from samples with which the blanks are associated. It is often impossible, however, to determine the association between certain blanks and data. In this case, compare the blank data with results from the entire sample data set. Use the guidelines in the following paragraphs when comparing sample concentrations with blank concentrations.

Blanks containing common laboratory contaminants. As discussed in the CLP SOW for Organics (EPA 1988c) and the Functional Guidelines for Organics (EPA 1988e), acetone, 2-butanone (or methyl ethyl ketone), methylene chloride, toluene, and the phthalate esters are considered by EPA to be common laboratory contaminants. In accordance with the Functional Guidelines for Organics (EPA 1988e) and the Functional Guidelines for Inorganics (EPA 1988d), if the blank contains detectable levels of common laboratory contaminants, then the sample results should be considered as positive results only if the concentrations in the sample exceed ten times the maximum amount detected in any blank. If the concentration of a common laboratory contaminant is less than ten times the blank concentration, then conclude that the chemical was not detected in the particular sample and, in accordance with EPA guidance, consider the blank-related concentrations of the chemical to be the quantitation limit for the chemical in that sample. Note that if all samples contain levels of a common laboratory contaminant that are less than ten times the level of contamination noted in the blank, then completely eliminate that chemical from the set of sample results.

TYPES OF BLANKS

Blanks are analytical quality control samples analyzed in the same manner as site samples. They are used in the measurement of contamination that has been introduced into a sample either (1) in the field while the samples were being collected or transported to the laboratory or (2) in the laboratory during sample preparation or analysis. Four types of blanks -- trip, field, laboratory calibration, and laboratory reagent (or method) -- are described below. A discussion on the water used for the blank also is provided.

Trip Blank. This type of blank is used to indicate potential contamination due to migration of volatile organic chemicals (VOCs) from the air on the site or in sample shipping containers, through the septum or around the lid of sampling vials, and into the sample. A trip blank consists of laboratory distilled, deionized water in a 40-ml glass vial sealed with a teflon septum. The blank accompanies the empty sample bottles to the field as well as the samples returning to the laboratory for analysis; it is not opened until it is analyzed in the lab with the actual site samples. The containers and labels for trip blanks should be the same as the containers and labels for actual samples, thus making the laboratory "blind" to the identity of the blanks.

Field Blank. A field blank is used to determine if certain field sampling or cleaning procedures (e.g., insufficient cleaning of sampling equipment) result in cross-contamination of site samples. Like the trip blank, the field blank is a sample of distilled, deionized water taken to the field with empty sample bottles and is analyzed in the laboratory along with the actual samples. Unlike the trip blank, however, the field blank sample is opened in the field and used as a sample would be (e.g., it is poured through cleaned sampling equipment or it is poured from container to container in the vicinity of a gas-powered pump). As with trip blanks, the field blanks' containers and labels should be the same as for actual samples.

Laboratory Calibration Blank. This type of blank is distilled, deionized water injected directly into an instrument without having been treated with reagents appropriate to the analytical method used to analyze actual site samples. This type of blank is used to indicate contamination in the instrument itself, or possibly in the distilled, deionized water.

Laboratory Reagent or Method Blank. This blank results from the treatment of distilled, deionized water with all of the reagents and manipulations (e.g., digestions or extractions) to which site samples will be subjected. Positive results in the reagent blank may indicate either contamination of the chemical reagents or the glassware and implements used to store or prepare the sample and resulting solutions. Although a laboratory following good laboratory practices will have its analytical processes under control, in some instances method blank contamination cannot be entirely eliminated.

Water Used for Blanks. For all the blanks described above, results are reliable only if the water comprising the blank was clean. For example, if the laboratory water comprising the trip blank was contaminated with VOCs prior to being taken to the field, then the source of VOC contamination in the trip blank cannot be isolated (see laboratory calibration blank).

Blanks containing chemicals that are not common laboratory contaminants. As discussed in the previously referenced guidance, if the blank contains detectable levels of one or more organic or inorganic chemicals that are not considered by EPA to be common laboratory contaminants (e.g., all other chemicals on the TCL), then consider site sample results as positive only if the concentration of the chemical in the site sample exceeds five times the maximum amount detected in any blank. Treat samples containing less than five times the amount in any blank as non-detects and, in accordance with EPA guidance, consider the blank-related chemical concentration to be the quantitation limit for the chemical in that sample. Again, note that if all samples contain levels of a TCL chemical that are less than five times the level of contamination noted in the blank, then completely eliminate that chemical from the set of sample results.

5.6 EVALUATION OF TENTATIVELY IDENTIFIED COMPOUNDS

Both the identity and reported concentration of a tentatively identified compound (TIC) is questionable (see the box on the next page for background on TICs). Two options for addressing TICs exist, depending on the relative number of TICs compared to non-TICs.

5.6.1 WHEN FEW TICs ARE PRESENT

When only a few TICs are present compared to the TAL and TCL chemicals, and no historical or other site information indicates that either a particular TIC may indeed be present at the site (e.g., because it may be a by-product of a chemical operation conducted when the site was active) or that the estimated concentration may be very high (i.e., the risk would be dominated by the TIC), then generally do not include the TICs in the risk assessment. Otherwise, follow the guidance provided in the next subsection. Consult with the RPM about omitting TICs from the quantitative risk assessment, and document reasons for excluding TICs in the risk assessment report.

TENTATIVELY IDENTIFIED COMPOUNDS

EPA's TCL may be a limited subset of the organic compounds that could actually be encountered at a particular site. Thus, although the CLP RAS requires the laboratory to analyze samples only for compounds on the TCL, the analysis of VOCs and SVOCs may indicate the presence of additional organic compounds not on the TCL. These additional compounds are shown by "peaks" on the chromatograms. (A chromatogram is a paper representation of the response of the instrument to the presence of a compound.) The CLP laboratory must attempt to identify the 30 highest peaks (10 VOCs and 20 SVOCs) using computerized searches of a library containing mass spectra (essentially "fingerprints" for particular compounds). When the mass spectra match to a certain degree, the compound (or general class of compound) is named; however, the assigned identity is in most cases highly uncertain. These compounds are called tentatively identified compounds (TICs).

The CLP SOW provides procedures to obtain a rough estimate of concentration of TICs. These estimates, however, are highly uncertain and could be orders of magnitude higher or lower than the actual concentration. For TICs, therefore, assigned identities may be inaccurate, and quantitation is certainly inaccurate. Due to these uncertainties, TIC information often is not provided with data summaries from site investigations. Additional sampling and analysis under SAS may reduce the uncertainty associated with TICs and, therefore, TIC information should be sought when it is absent from data summaries.

5.6.2 WHEN MANY TICs ARE PRESENT

If many TICs are present relative to the TAL and TCL compounds identified, or if TIC concentrations appear high or site information indicates that TICs are indeed present, then further evaluation of TICs is necessary. If sufficient time is available, use SAS to confirm the identity and to positively and reliably measure the concentrations of TICs prior to their use in the risk assessment. If SAS methods to identify and measure TICs are unavailable, or if there is insufficient time to use SAS, then the TICs should be included as chemicals of potential concern in the risk assessment and the uncertainty in both identity and concentration should be noted (unless information exists to indicate that the TICs are not present).

5.7 COMPARISON OF SAMPLES WITH BACKGROUND

In some cases, a comparison of sample concentrations with background concentrations (e.g., using the geometric mean concentrations of the two data sets) is useful for identifying the non-site-related chemicals that are found at or near the site. If background risk might be a concern, it should be calculated separately from site-related risk. Often, however, the comparison of samples with background is unnecessary because of the low risk usually posed by the background chemicals compared to site-related chemicals.

As discussed in Chapter 4, information collected during the RI can provide information on two types of background chemicals: (1) naturally occurring chemicals that have not been influenced by humans and (2) chemicals that are present due to anthropogenic sources. Either type of background chemical can be either localized or ubiquitous.

Information on background chemicals may have been obtained by the collection of site-specific background samples and/or from other sources (e.g., County Soil Conservation Service surveys, United States Geological Survey [USGS] reports). As discussed in Chapter 4, background

concentrations should be from the site or the vicinity of the site.

5.7.1 USE APPROPRIATE BACKGROUND DATA

Background samples collected during the site investigation should not be used if they were obtained from areas influenced or potentially influenced by the site. Instead, the literature sources mentioned in the previous paragraph may be consulted to determine background levels of chemicals in the vicinity of the site. Care must be taken in using literature sources, because the data contained therein might represent nationwide variation in a particular parameter rather than variation typical of the geographic region or geological setting in which the site is located. For example, a literature source providing concentrations of chemicals in ground water on a national scale may show a wide range of concentrations that is not representative of the variation in concentrations that would be expected at a particular site.

5.7.2 IDENTIFY STATISTICAL METHODS

In cases where background comparisons will be made, any statistical methods that will be used should be identified prior to the collection of samples (see Chapter 4). Guidance documents and reports that are available to aid in background comparison are listed in Section 4.4.3. Prior to conducting the steps discussed in the next two subsections, the RPM should be consulted to determine the type of comparison to be made, if any. Both a justification for eliminating chemicals based on a background comparison and a brief overview of the type of comparison conducted should be included in the risk assessment report.

5.7.3 COMPARE CHEMICAL CONCENTRATIONS WITH NATURALLY OCCURRING LEVELS

As defined previously, naturally occurring levels are levels of chemicals that are present under ambient conditions and that have not been increased by anthropogenic sources. If inorganic chemicals are present at the site at naturally occurring levels, they may be eliminated from the quantitative risk assessment. In some cases, however, background concentrations may present a significant risk, and, while cleanup may or may not eliminate this risk, the background risk may be an important site characteristic to those exposed. The RPM will always have the option to consider the risk posed by naturally occurring background chemicals separately.

In general, comparison with naturally occurring levels is applicable only to inorganic chemicals, because the majority of organic chemicals found at Superfund sites are not naturally occurring (even though they may be ubiquitous). The presence of organic chemicals in background samples collected during a site investigation actually may indicate that the sample was collected in an area influenced by site contamination and therefore does not qualify as a true background sample. Such samples should instead be included with other site samples in the risk assessment. Unless a very strong case can be made for the natural occurrence of an organic chemical, do not eliminate it from the quantitative risk assessment for this reason.

5.7.4 COMPARE CHEMICAL CONCENTRATIONS WITH ANTHROPOGENIC LEVELS

Anthropogenic levels are ambient concentrations resulting from human (non-site) sources. Localized anthropogenic background is often caused by a point source such as a nearby factory. Ubiquitous anthropogenic background is often from nonpoint sources such as automobiles. In general, do not eliminate anthropogenic chemicals because, at many sites, it is extremely difficult to conclusively show at this stage of the site investigation that such chemicals are present at the site due to operations not related to the site or the surrounding area.

Often, anthropogenic background chemicals can be identified and considered separately during or at the end of the risk assessment. These chemicals also can be omitted entirely from the risk assessment, but, as discussed for natural background, they may present a significant risk. Omitting anthropogenic background chemicals

from the risk assessment could result in the loss of important information for those potentially exposed.

5.8 DEVELOPMENT OF A SET OF CHEMICAL DATA AND INFORMATION FOR USE IN THE RISK ASSESSMENT

After the evaluation of data is complete as specified in previous sections, a list of the samples (by medium) is made that will be used to estimate exposure concentrations, as discussed in Chapter 6 of this guidance. In addition, as shown in the flowchart in Exhibit 5-1, a list of chemicals of potential concern (also by medium) will be needed for the quantitative risk assessment. This list should include chemicals that were:

(1) positively detected in at least one CLP sample (RAS or SAS) in a given medium, including (a) chemicals with no qualifiers attached (excluding samples with unusually high detection limits), and (b) chemicals with qualifiers attached that indicate known identities but unknown concentrations (e.g., J-qualified data);

(2) detected at levels significantly elevated above levels of the same chemicals detected in associated blank samples;

(3) detected at levels significantly elevated above naturally occurring levels of the same chemicals;

(4) only tentatively identified but either may be associated with the site based on historical information or have been confirmed by SAS; and/or

(5) transformation products of chemicals demonstrated to be present.

Chemicals that were not detected in samples from a given medium (i.e., non-detects) but that may be present at the site also may be included in the risk assessment if an evaluation of the risks potentially present at the detection limit is desired.

5.9 FURTHER REDUCTION IN THE NUMBER OF CHEMICALS (OPTIONAL)

For certain sites, the list of potentially site-related chemicals remaining after quantitation limits, qualifiers, blank contamination, and background have been evaluated may be lengthy. Carrying a large number of chemicals through a quantitative risk assessment may be complex, and it may consume significant amounts of time and resources. The resulting risk assessment report, with its large, unwieldy tables and text, may be difficult to read and understand, and it may distract from the dominant risks presented by the site. In these cases, the procedures discussed in this section -- using chemical classes, frequency of detection, essential nutrient information, and a concentration-toxicity screen -- may be used to further reduce the number of chemicals of potential concern in each medium.

If conducting a risk assessment on a large number of chemicals is feasible (e.g., because of adequate computer capability), then the procedures presented in this section should not be used. Rather, the most important chemicals (e.g., those presenting 99 percent of the risk) -- identified after the risk assessment -- could be presented in the main text of the report, and the remaining chemicals could be presented in the appendices.

5.9.1 CONDUCT INITIAL ACTIVITIES

Several activities must be conducted before implementing any of the procedures described in this section: (1) consult with the RPM; (2) consider how the rationale for the procedure should be documented; (3) examine historical information on the site; (4) consider concentration and toxicity of the chemicals; (5) examine the mobility, persistence, and bioaccumulation potential of the chemicals; (6) consider special exposure routes; (7) consider the treatability of the chemicals; (8) examine applicable or relevant and appropriate requirements (ARARs); and (9) examine the need for the procedures. These activities are described below.

Consultation with the RPM. If a large number of chemicals are of potential concern at a particular

site, the RPM should be consulted. Approval by the RPM must be obtained prior to the elimination of chemicals based on any of these procedures. The concentration-toxicity screen in particular may be needed only in rare instances.

Documentation of rationale. The rationale for eliminating chemicals from the quantitative risk assessment based on the procedures discussed below must be clearly stated in the risk assessment report. This documentation, and its possible defense at a later date, could be fairly resource-intensive. If a continuing need to justify this step is expected, then any plans to eliminate chemicals should be reconsidered.

Historical information. Chemicals reliably associated with site activities based on historical information generally should not be eliminated from the quantitative risk assessment, even if the results of the procedures given in this section indicate that such an elimination is possible.

Concentration and toxicity. Certain aspects of concentration and toxicity of the chemicals also must be considered prior to eliminating chemicals based on the results of these procedures. For example, before eliminating potentially carcinogenic chemicals, the weight-of-evidence classification should be considered in conjunction with the concentrations detected at the site. It may be practical and conservative to retain a chemical that was detected at low concentrations if that chemical is a Group A carcinogen. (As discussed in detail in Chapter 7, the weight-of-evidence classification is an indication of the quality and quantity of data underlying a chemical's designation as a potential human carcinogen.)

Mobility, persistence, and bioaccumulation. Three factors that must be considered when implementing these procedures are the mobility, persistence, and bioaccumulation of the chemicals. For example, a highly volatile (i.e., mobile) chemical such as benzene, a long-lived (i.e., persistent) chemical such as dioxin, or a readily taken-up and concentrated (i.e., bioaccumulated) chemical such as DDT, probably should remain in the risk assessment. These procedures do not explicitly include a mobility, persistence, or bioaccumulation component, and therefore the risk assessor must pay special attention to these factors.

Special exposure routes. For some chemicals, certain exposure routes need to be considered carefully before using these procedures. For example, some chemicals are highly volatile and may pose a significant inhalation risk due to the home use of contaminated water, particularly for showering. The procedures described in this section may not account for exposure routes such as this.

Treatability. Some chemicals are more difficult to treat than others and as a result should remain as chemicals of potential concern because of their importance during the selection of remedial alternatives.

ARARs. Chemicals with ARARs (including those relevant to land ban compliance) usually are not appropriate for exclusion from the quantitative risk assessment based on the procedures in this section. This may, however, depend in part on how the chemicals' site concentrations in specific media compare with their ARAR concentrations for these media.

Need for procedures. Quantitative evaluation of all chemicals of potential concern is the most thorough approach in a risk assessment. In addition, the time required to implement and defend the selection procedures discussed in this section may exceed the time needed to simply carry all the chemicals of potential concern through the risk assessment. Usually, carrying all chemicals of potential concern through the risk assessment will not be a difficult task, particularly given the widespread use of computer spreadsheets to calculate exposure concentrations of chemicals and their associated risks. Although the tables that result may indeed be large, computer spreadsheets significantly increase the ability to evaluate a number of chemicals in a relatively short period of time. For these reasons, the procedures discussed here may be needed only in rare instances. As previously stated, the approval of these procedures by the RPM must be obtained prior to implementing any of these optional screening procedures at a particular site.

5.9.2 GROUP CHEMICALS BY CLASS

At times, toxicity values to be used in characterizing risks are available only for certain chemicals within a chemical class. For example, of the polycyclic aromatic hydrocarbons (PAHs) considered to be potential carcinogens, a slope factor currently is available (i.e., as this manual went to press) for benz(a)pyrene only. In these cases, rather than eliminating the other chemicals within the class from quantitative evaluation because of a lack of toxicity values, it may be useful to group data for such a class of chemicals (e.g., according to structure-activity relationships or other similarities) for consideration in later sections of the risk assessment. For example, the concentrations of only one group of chemicals (e.g., carcinogenic PAHs) would be considered rather than concentrations of each of the seven carcinogenic PAHs currently on the TCL.

To group chemicals by class, concentrations of chemicals within each class are summed according to procedures discussed in Chapter 6 of this guidance. Later in the risk assessment, this chemical class concentration would be used to characterize risk using toxicity values (i.e., RfDs or slope factors) associated with one of the chemicals in the particular class.

Three notes of caution when grouping chemicals should be considered: (1) do not group solely by toxicity characteristics; (2) do not group all carcinogenic chemicals or all noncarcinogenic chemicals without regard to structure-activity or other chemical similarities; and (3) discuss in the risk assessment report that grouping can produce either over- or under-estimates of the true risk.

5.9.3 EVALUATE FREQUENCY OF DETECTION

Chemicals that are infrequently detected may be artifacts in the data due to sampling, analytical, or other problems, and therefore may not be related to site operations or disposal practices. Consider the chemical as a candidate for elimination from the quantitative risk assessment if: (1) it is detected infrequently in one or perhaps two environmental media, (2) it is not detected in any other sampled media or at high concentrations, and (3) there is no reason to believe that the chemical may be present. Available modeling results may indicate whether monitoring data that show infrequently detected chemicals are representative of only their sampling locations or of broader areas. Because chemical concentrations at a site are spatially variable, the risk assessor can use modeling results to project infrequently detected chemical concentrations over broader areas when determining whether the subject chemicals are relevant to the overall risk assessment. Judicious use of modeling to supplement available monitoring data often can minimize the need for the RPM to resort to arbitrarily setting limits on inclusion of infrequently detected chemicals in the risk assessment. Any detection frequency limit to be used (e.g., five percent) should be approved by the RPM prior to using this screen. If, for example, a frequency of detection limit of five percent is used, then at least 20 samples of a medium would be needed (i.e., one detect in 20 samples equals a five percent frequency of detection).

In addition to available monitoring data and modeling results, the risk assessor will need to consider other relevant factors (e.g., presence of sensitive subpopulations) in recommending appropriate site-specific limits on inclusion of infrequently detected chemicals in the quantitative risk assessment. For example, the risk assessor should consider whether the chemical is expected to be present based on historical data or any other relevant information (e.g., known degradation products of chemicals present at the site, modeling results). Chemicals expected to be present should not be eliminated. (See the example of chemicals with similar transport and fate characteristics in Section 5.3.5.)

The reported or modeled concentrations and locations of chemicals should be examined to check for hotspots, which may be especially important for short-term exposures and which therefore should not be eliminated from the risk assessment. Always consider detection of particular chemicals in all sampled media because some media may be sources of contamination for other media. For example, a chemical that is infrequently detected in soil (a potential ground-water contamination source) probably should not be eliminated as a site

contaminant if the same chemical is frequently detected in ground water. In addition, infrequently detected chemicals with concentrations that greatly exceed reference concentrations should not be eliminated.

5.9.4 EVALUATE ESSENTIAL NUTRIENTS

Chemicals that are (1) essential human nutrients, (2) present at low concentrations (i.e., only slightly elevated above naturally occurring levels), and (3) toxic only at very high doses (i.e., much higher than those that could be associated with contact at the site) need not be considered further in the quantitative risk assessment. Examples of such chemicals are iron, magnesium, calcium, potassium, and sodium.

Prior to eliminating such chemicals from the risk assessment, they must be shown to be present at levels that are not associated with adverse health effects. The determination of acceptable dietary levels for essential nutrients, however, often is very difficult. Literature values concerning acceptable dietary levels may conflict and may change fairly often as new studies are conducted. For example, arsenic -- a potential carcinogen -- is considered by some scientists to be an essential nutrient based on animal experiments; however, acceptable dietary levels are not well known (EPA 1988f). Therefore, arsenic should be retained in the risk assessment, even though it may be an essential nutrient at undefined dietary levels. Another example of a nutrient that is difficult to characterize is sodium. Although an essential element in the diet, certain levels of sodium may be associated with blood pressure effects in some sensitive individuals (although data indicating an association between sodium in drinking water and hypertension are inadequate [EPA 1987]).

Another problem with determining acceptable dietary levels for essential nutrients is that nutrient levels often are presented in the literature as concentrations within the human body (e.g., blood levels). To identify an essential nutrient concentration to be used for comparison with concentrations in a particular medium at a site, blood (or other tissue) levels of the chemical from the literature must be converted to concentrations in the media of concern for the site (e.g., soil, drinking water).

For these reasons, it may not be possible to compare essential nutrient concentrations with site concentrations in order to eliminate essential nutrient chemicals. In general, only essential nutrients present at low concentrations (i.e., only slightly elevated above background) should be eliminated to help ensure that chemicals present at potentially toxic concentrations are evaluated in the quantitative risk assessment.

5.9.5 USE A CONCENTRATION-TOXICITY SCREEN

The objective of this screening procedure is to identify the chemicals in a particular medium that -- based on concentration and toxicity -- are most likely to contribute significantly to risks calculated for exposure scenarios involving that medium, so that the risk assessment is focused on the "most significant" chemicals.

Calculate individual chemical scores. Two of the most important factors when determining the potential effect of including a chemical in the risk assessment are its measured concentrations at the site and its toxicity. Therefore, in this screening procedure, each chemical in a medium is first scored according to its concentration and toxicity to obtain a risk factor (see the box below). Separate scores are calculated for each medium being evaluated.

INDIVIDUAL CHEMICAL SCORES

$$Rij = (C_{ij})(T_{ij})$$

where:

R_{ij} = risk factor for chemical i in medium j;

C_{ij} = concentration of chemical i in medium j; and

T_{ij} = toxicity value for chemical i in medium j (i.e., either the slope factor or 1/RfD).

The units for the risk factor R_{ij} depend on the medium being screened. In general, the absolute units do not matter, as long as units among chemicals in a medium are the same. To be conservative, the concentration used in the above equation should be the maximum detected concentration determined according to procedures discussed in Chapter 6, and toxicity values should be obtained in accordance with the procedures discussed in Chapter 7.

Chemicals without toxicity values cannot be screened using this procedure. Such chemicals should always be discussed in the risk assessment as chemicals of potential concern; they should not be eliminated from the risk assessment. Guidance concerning chemicals without toxicity values is provided in Chapter 7.

For some chemicals, both oral and inhalation toxicity values are available. In these cases, the more conservative toxicity values (i.e., ones yielding the larger risk factor when used in the above equation) usually should be used. If only one exposure route is likely for the medium being evaluated, then the toxicity values corresponding to that exposure route should be used.

Calculate total chemical scores (per medium). Chemical-specific risk factors are summed to obtain the total risk factor for all chemicals of potential concern in a medium (see the box on this page). A separate R_j will be calculated for carcinogenic and noncarcinogenic effects. The ratio of the risk factor for each chemical to the total risk factor (i.e., R_{ij}/R_j) approximates the relative risk for each chemical in medium j.

Eliminate chemicals. After carefully considering the factors discussed previously in this subsection, eliminate from the risk assessment chemicals with R_{ij}/R_j ratios that are very low compared with the ratios of other chemicals in the medium. The RPM may wish to specify a limit for this ratio (e.g., 0.01; a lower fraction would be needed if site risks are expected to be high). A chemical that contributes less than the specified fraction of the total risk factor for each medium would not be considered further in the risk assessment for that medium. Chemicals exceeding the limit would be considered likely to contribute significantly to risks, as calculated in subsequent stages of the risk assessment. This screening procedure could greatly reduce the number of chemicals carried through a risk assessment, because in many cases only a few chemicals contribute significantly to the total risk for a particular medium.

TOTAL CHEMICAL SCORES

$$R_j = R_{1j} + R_{2j} + R_{3j} + \ldots + R_{ij}$$

where

R_j =total risk factor for medium j; and

$R_{1j} + \ldots + R_{ij}$ =risk factors for chemicals 1 through i in medium j.

The risk factors developed in this screening procedure are to be used only for potential reduction of the number of chemicals carried through the risk assessment and have no meaning outside of the context of the screening procedure. They should not be considered as a quantitative measure of a chemical's toxicity or risk or as a substitute for the risk assessment procedures discussed in Chapters 6, 7, and 8 of this guidance.

5.10 SUMMARY AND PRESENTATION OF DATA

The section of the risk assessment report summarizing the results of the data collection and evaluation should be titled "Identification of Chemicals of Potential Concern" (see Chapter 9). Information in this section should be presented in ways that readily support the calculation of exposure concentrations in the exposure assessment portion of the risk assessment. Exhibits 5-6 and 5-7 present examples of tables to be included in this section of the risk assessment report.

EXHIBIT 5-6

EXAMPLE OF TABLE FORMAT FOR PRESENTING CHEMICALS SAMPLED IN SPECIFIC MEDIA

Table X
Chemicals Sampled in Medium Y
(and in Operable Unit Z, if appropriate)
Name of Site, Location of Site

Chemical	Frequency of Detection[a]	Range of Sample Quantitation Limits (units)	Range of Detected Concentrations (units)	Background Levels
Chemical A	3/25	5 - 50	320 - 4600	100 - 140
* Chemical B	25/25	1 - 32	16 - 72	--

-- = Not available.

* Identified as a chemical of potential concern based on evaluation of data according to procedures described in text of report.

[a] Number of samples in which the chemical was positively detected over the number of samples available.

EXHIBIT 5-7

EXAMPLE OF TABLE FORMAT FOR SUMMARIZING CHEMICALS OF POTENTIAL CONCERN IN ALL MEDIA SAMPLED

Table W
Summary of Chemicals of
Potential Concern at Site X, Location Y
(and in Operable Unit Z, if appropriate)

Chemical	Concentration				
	Soils (mg/kg)	Ground Water (ug/L)	Surface Water (ug/L)	Sediments (ug/kg)	Air (ug/m^3)
Chemical A	5 - 1,100	--	2 - 30	--	--
Chemical B	0.5 - 64	5 - 92	--	100 - 45,000	--
Chemical C	--	15 - 890	50 - 11,000	--	--
Chemical D	2 - 12	--	--	--	0.1 - 940

-- = Not available.

5.10.1 SUMMARIZE DATA COLLECTION AND EVALUATION RESULTS IN TEXT

In the introduction for this section of the risk assessment report, clearly discuss in bullet form the steps involved in data evaluation. If the optional screening procedure described in Section 5.9 was used in determining chemicals of potential concern, these steps should be included in the introduction. If both historical data and current data were used in the data evaluation, state this in the introduction. Any special site-specific considerations in collecting and evaluating the data should be mentioned. General uncertainties concerning the quality associated with either the collection or the analysis of samples should be discussed so that the potential effects of these uncertainties on later sections of the risk assessment can be determined.

In the next part of the report, discuss the samples from each medium selected for use in quantitative risk assessment. Provide information concerning the sample collection methods used (e.g., grab, composite) as well as the number and location of samples. If this information is provided in the RI report, simply refer to the appropriate sections. If any samples (e.g., field screening/analytical samples) were excluded specifically from the quantitative risk assessment prior to evaluating the data, document this along with reasons for the exclusion. Again, remember that such samples, while not used in the quantitative risk assessment, may be useful for qualitative discussions and therefore should not be entirely excluded from the risk assessment.

Discuss the data evaluation either by medium, by medium within each operable unit (if the site is sufficiently large to be divided into specific operable units), or by discrete areas within each medium in an operable unit. For each medium, if several source areas with different types and concentrations of chemicals exist, then the medium-specific discussion for each source area may be separate. Begin the discussion with those media (e.g., wastes, soils) that are potential sources of contamination for other media (e.g., ground water, surface water/sediments). If no samples or data were available for a particular medium, discuss this in the text. For soils data, discuss surface soil results separately from those of subsurface soils. Present ground-water results by aquifer if more than one aquifer was sampled. Discuss surface water/sediment results by the specific surface water body sampled.

For each medium, identify in the report the chemicals for which samples were analyzed, and list the analytes that were detected in at least one sample. If any detected chemicals were eliminated from the quantitative risk assessment based on evaluation of data (i.e., based on evaluation of data quality, background comparisons, and the optional screening procedures, if used), provide reasons for the elimination in the text (e.g., chemical was detected in blanks at similar concentrations to those detected in samples or chemical was infrequently detected).

The final subsection of the text is a discussion of general trends in the data results. For example, the text may mention (1) whether concentrations of chemicals of potential concern in most media were close to the detection limits or (2) trends concerning chemicals detected in more than one medium or in more than one operable unit at the site. In addition, the location of hot spots should be discussed, as well as any noticeable trends apparent from sampling results at different times.

5.10.2 SUMMARIZE DATA COLLECTION AND EVALUATION RESULTS IN TABLES AND GRAPHICS

As shown in Exhibit 5-6, a separate table that includes all chemicals detected in a medium can be provided for each medium sampled at a hazardous waste site or for each medium within an operable unit at a site. Chemicals that have been determined to be of potential concern based on the data evaluation should be designated in the table with an asterisk to the left of the chemical name.

For each chemical, present the frequency of detection in a certain medium (i.e., the number of times a chemical was detected over the total number of samples considered) and the range of detected or quantified values in the samples. Do not present the QL or similar indicator of a minimum level (e.g., <10 mg/L, ND) as the lower end of the range; instead, the lower and upper bound of the range should be the minimum and maximum detected values, respectively. The range of reported QLs obtained for each chemical in various samples should be provided

in a separate column. Note that these QLs should be sample-specific; CRQLs, MDLs, or other types of non-sample-specific values should be provided only when SQLs are not available. Note that the range of QLs would not include any limit values (e.g., unusually high QLs) eliminated based on the guidance in Section 5.3. Finally, naturally occurring concentrations of chemicals used in comparing sample concentrations may be provided in a separate column. The source of these naturally occurring levels should be provided in a footnote. List the identity of the samples used in determining concentrations presented in the table in an appropriate footnote.

The final table in this section is a list of the chemicals of potential concern presented by medium at the site or by medium within each operable unit at the site. A sample table format is presented in Exhibit 5-7.

Another useful type of presentation of chemical concentration data is the isopleth (not shown). This graphic characterizes the monitored or modeled concentrations of chemicals at a site and illustrates the spatial pattern of contamination.

ENDNOTE FOR CHAPTER 5

1. Note that the values in this example are for illustration purposes only. Many CRQLs and CRDLs are in the process of being lowered, and the RfDs and slope factors may have changed.

REFERENCES FOR CHAPTER 5

Environmental Protection Agency (EPA). 1984. Methods for Organic Chemical Analysis of Municipal and Industrial Wastewater (EPA 600 Methods) as presented in 40 CFR Part 136, Guidelines Establishing Test Procedures for the Analysis of Pollutants Under the Clean Water Act.

- Used to determine chemicals present in municipal and industrial wastewater as provided under the Clean Water Act. Analytical methods for priority pollutants, including sample preparation, reagents, calibration procedures, QA/QC analytical procedures, and calculations.

Environmental Protection Agency (EPA). 1986. Test Methods for Evaluating Solid Waste (SW-846): Physical/Chemical Methods. Office of Solid Waste.

- Provides analytical procedures to test solid waste to determine if it is a hazardous waste as defined under RCRA. Contains information for collecting solid waste samples and for determining reactivity, corrosivity, ignitability, composition of waste, and mobility of waste components.

Environmental Protection Agency (EPA). 1987. Drinking Water; Proposed Substitution of Contaminants and Proposed List of Additional Substances Which May Require Regulation Under the Safe Drinking Water Act. 52 Federal Register 25720 (July 8, 1987).

Environmental Protection Agency (EPA). 1988a. User's Guide to the Contract Laboratory Program. Office of Emergency and Remedial Response.

- Provides requirements and analytical procedures of the CLP protocols developed from technical caucus recommendations for both organic and inorganic analysis. Contains information on CLP objectives and orientation, CLP structure, description of analytical services, utilization of analytical services, auxiliary support services, and program quality assurance.

Environmental Protection Agency (EPA). 1988b. Contract Laboratory Program Statement of Work for Inorganics Analysis: Multi-media, Multi-concentration. Office of Emergency and Remedial Response. SOW No. 788.

- Provides procedures required by EPA for analyzing hazardous waste disposal site samples (aqueous and solid) for inorganic chemicals (25 elements plus cyanide). Contains analytical, document control, and quality assurance/quality control procedures.

Environmental Protection Agency (EPA). 1988c. Contract Laboratory Program Statement of Work for Organics Analysis: Multi-media, Multi-concentration. Office of Emergency and Remedial Response. SOW No. 288.

- Provides procedures required by EPA for analyzing aqueous and solid hazardous waste samples for 126 volatile, semi-volatile, pesticide, and PCB chemicals. Contains analytical, document control, and quality assurance/quality control procedures.

Environmental Protection Agency (EPA). 1988d. Laboratory Data Validation Functional Guidelines for Evaluating Inorganics Analysis. Office of Emergency and Remedial Response.

- Provides guidance in laboratory data evaluation and validation for hazardous waste site samples analyzed under the EPA CLP program. Aids in determining data problems and shortcomings and potential actions to be taken.

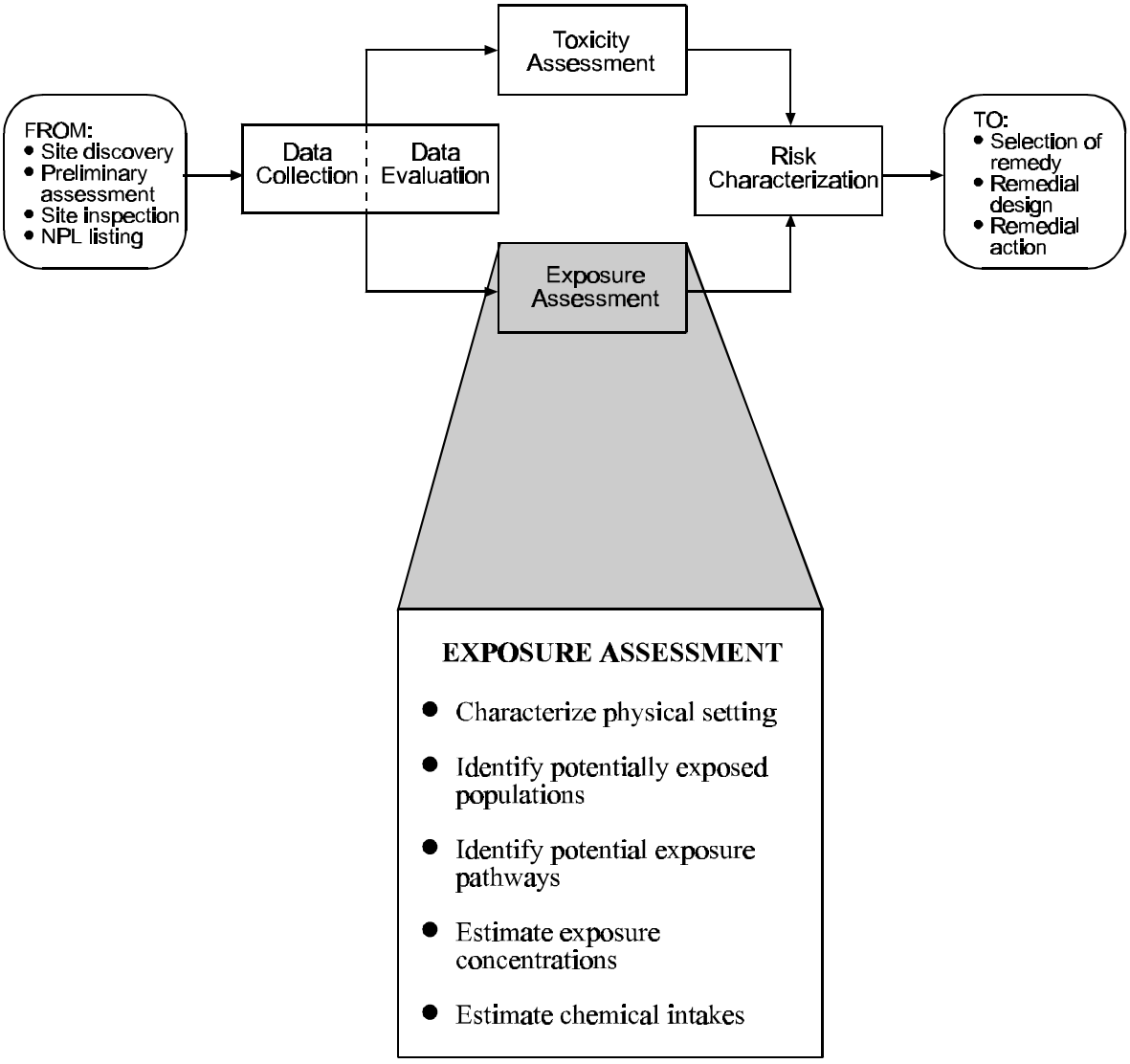
Environmental Protection Agency (EPA). 1988e. Laboratory Data Validation Functional Guidelines for Evaluating Organics Analysis (Functional Guidelines for Organics). Office of Emergency and Remedial Response.

- Provides guidance in laboratory data evaluation and validation for hazardous waste site samples analyzed under the EPA CLP program. Aids in determining data problems and shortcomings and potential actions to be taken.

Environmental Protection Agency (EPA). 1988f. Special Report on Ingested Inorganic Arsenic; Skin Cancer; Nutritional Essentiality. Risk Assessment Forum. EPA 625/3-87/013.

- Technical report concerning the health effects of exposure to ingested arsenic. Includes epidemiologic studies suitable for dose-response evaluation from Taiwan, Mexico, and Germany. Also includes discussions on pathological characteristics and significance of arsenic-induced skin lesions, genotoxicity of arsenic, metabolism and distribution, dose-response estimates for arsenic ingestion and arsenic as an essential nutrient.

CHAPTER 6
EXPOSURE ASSESSMENT



CHAPTER 6

EXPOSURE ASSESSMENT

This chapter describes the procedures for conducting an exposure assessment as part of the baseline risk assessment process at Superfund sites. The objective of the exposure assessment is to estimate the type and magnitude of exposures to the chemicals of potential concern that are present at or migrating from a site. The results of the exposure assessment are combined with chemical-specific toxicity information to characterize potential risks.

The procedures and information presented in this chapter represent some new approaches to exposure assessment as well as a synthesis of currently available exposure assessment guidance and information published by EPA. Throughout this chapter, relevant exposure assessment documents are referenced as sources of more detailed information supporting the exposure assessment process.

6.1 BACKGROUND

Exposure is defined as the contact of an organism (humans in the case of health risk assessment) with a chemical or physical agent (EPA 1988a). The magnitude of exposure is determined by measuring or estimating the amount of an agent available at the exchange boundaries (i.e., the lungs, gut, skin) during a specified time period. Exposure assessment is the determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure. Exposure assessments may consider past, present, and future exposures, using varying assessment techniques for each phase. Estimates of current exposures can be based on measurements or models of existing conditions, those of future exposures can be based on models of future conditions, and those of past exposures can be based on measured or modeled past concentrations or measured chemical concentrations in tissues. Generally, Superfund exposure assessments are concerned with current and future exposures. If human monitoring is planned to assess current or past exposures, the Agency for Toxic Substances and Disease Registry (ATSDR) should be consulted to take the lead in conducting these studies and in assessing the current health status of the people near the site based on the monitoring results.

6.1.1 COMPONENTS OF AN EXPOSURE ASSESSMENT

The general procedure for conducting an exposure assessment is illustrated in Exhibit 6-1. This procedure is based on EPA's published *Guidelines for Exposure Assessment* (EPA 1986a) and on other related guidance (EPA 1988a, 1988b). It is an adaptation of the generalized exposure assessment process to the particular needs of Superfund site risk assessments. Although some exposure assessment activities may have been started earlier (e.g., during RI/FS scoping or even before the RI/FS process began), the detailed exposure assessment process begins after the chemical data have been collected and validated and the chemicals of potential concern have been selected (see Chapter 5, Section 5.3.3). The exposure assessment proceeds with the following steps.

ACRONYMS FOR CHAPTER 6

ATSDR = Agency for Toxic Substances and Disease Registry
BCF = Bioconcentration Factor
CDI = Chronic Daily Intake
CEAM = Center for Exposure Assessment Modeling
NOAA = National Oceanographic and Atmospheric Administration
NTGS = National Technical Guidance Studies
OAQPS = Office of Air Quality Planning and Standards
RME = Reasonable Maximum Exposure
SDI = Subchronic Daily Intake
SEAM = Superfund Exposure Assessment Manual
USGS = U.S. Geological Survey

DEFINITIONS FOR CHAPTER 6

Absorbed Dose. The amount of a substance penetrating the exchange boundaries of an organism after contact. Absorbed dose is calculated from the intake and the absorption efficiency. It usually is expressed as mass of a substance absorbed into the body per unit body weight per unit time (e.g., mg/kg-day).

Administered Dose. The mass of a substance given to an organism and in contact with an exchange boundary (e.g., gastrointestinal tract) per unit body weight per unit time (e.g., mg/kg-day).

Applied Dose. The amount of a substance given to an organism, especially through dermal contact.

Chronic Daily Intake (CDI). Exposure expressed as mass of a substance contacted per unit body weight per unit time, averaged over a long period of time (as a Superfund program guideline, seven years to a lifetime).

Contact Rate. Amount of medium (e.g., ground water, soil) contacted per unit time or event (e.g. liters of water ingested per day).

Exposure. Contact of an organism with a chemical or physical agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut) and available for absorption.

Exposure Assessment. The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure.

Exposure Event. An incident of contact with a chemical or physical agent. An exposure event can be defined by time (e.g., day, hour) or by the incident (e.g., eating a single meal of contaminated fish).

Exposure Pathway. The course a chemical or physical agent takes from a source to an exposed organism. An exposure pathway describes a unique mechanism by which an individual or population is exposed to chemicals or physical agents at or originating from a site. Each exposure pathway includes a source or release from a source, an exposure point, and an exposure route. If the exposure point differs from the source, a transport/exposure medium (e.g., air) or media (in cases of intermedia transfer) also is included.

Exposure Point. A location of potential contact between an organism and a chemical or physical agent.

Exposure Route. The way a chemical or physical agent comes in contact with an organism (e.g., by ingestion, inhalation, dermal contact).

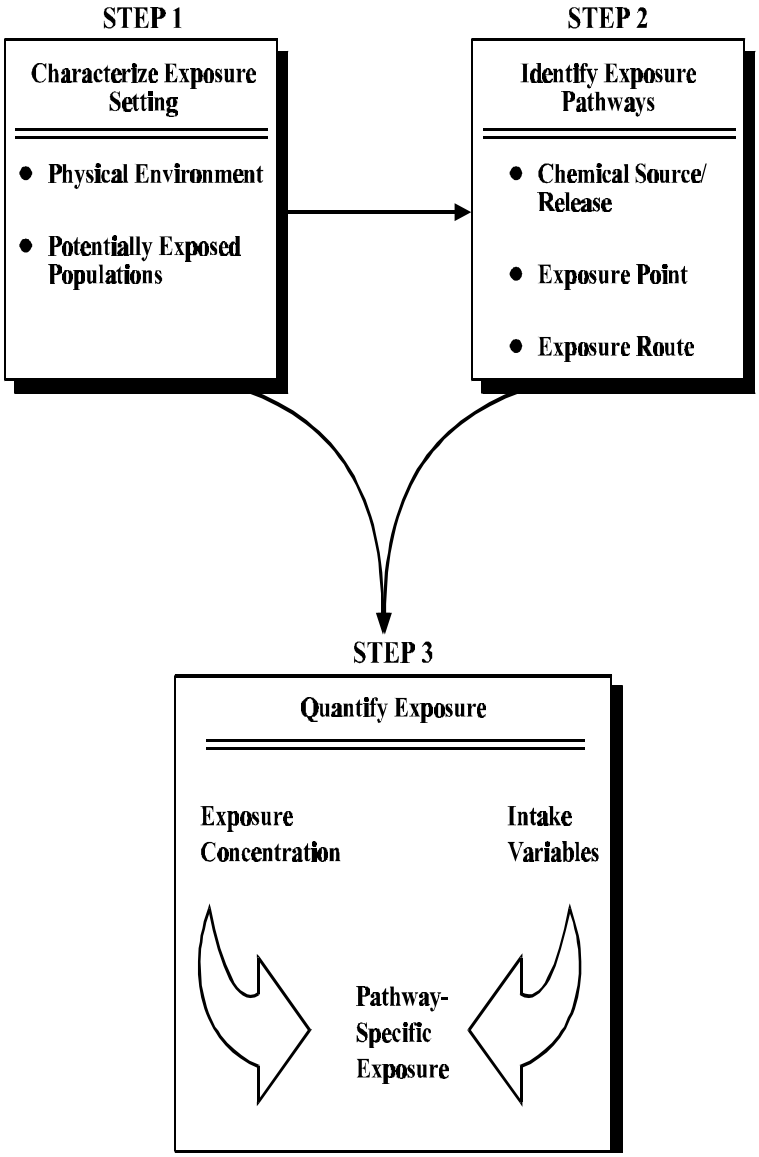
Intake. A measure of exposure expressed as the mass of a substance in contact with the exchange boundary per unit body weight per unit time (e.g., mg chemical/kg body weight-day). Also termed the normalized exposure rate equivalent to administered dose.

Lifetime Average Daily Intake. Exposure expressed as mass of a substance contacted per unit body weight per unit time, averaged over a lifetime.

Subchronic Daily Intake (SDI). Exposure expressed as mass of a substance contacted per unit body weight per unit time, averaged over a portion of a lifetime (as a Superfund program guideline, two weeks to seven years).

Step 1 -- Characterization of exposure setting (Section 6.2). In this step, the assessor characterizes the exposure setting with respect to the general physical characteristics of the site and the characteristics of the populations on and near the site. Basic site characteristics such as climate, vegetation, ground-water hydrology, and the presence and location of surface water are identified in this step. Populations also are identified and are described with respect to those characteristics that influence exposure, such as location relative to the site, activity patterns, and the presence of sensitive subpopulations. This step considers the characteristics of the current population, as well as those of any potential future populations that may differ under an alternate land use.

EXHIBIT 6-1
THE EXPOSURE ASSESSMENT PROCESS



Step 2 -- Identification of exposure pathways (Section 6.3). In this step, the exposure assessor identifies those pathways by which the previously identified populations may be exposed. Each exposure pathway describes a unique mechanism by which a population may be exposed to the chemicals at or originating from the site. Exposure pathways are identified based on consideration of the sources, releases, types, and locations of chemicals at the site; the likely environmental fate (including persistence, partitioning, transport, and intermedia transfer) of these chemicals; and the location and activities of the potentially exposed populations. Exposure points (points of potential contact with the chemical) and routes of exposure (e.g., ingestion, inhalation) are identified for each exposure pathway.

Step 3 -- Quantification of exposure (Section 6.4). In this step, the assessor quantifies the magnitude, frequency and duration of exposure for each pathway identified in Step 2. This step is most often conducted in two stages: estimation of exposure concentrations and calculation of intakes.

Estimation of exposure concentrations (Section 6.5). In this part of step 3, the exposure assessor determines the concentration of chemicals that will be contacted over the exposure period. Exposure concentrations are estimated using monitoring data and/or chemical transport and environmental fate models. Modeling may be used to estimate future chemical concentrations in media that are currently contaminated or that may become contaminated, and current concentrations in media and/or at locations for which there are no monitoring data.

Calculation of intakes (Section 6.6). In this part of step 3, the exposure assessor calculates chemical-specific exposures for each exposure pathway identified in Step 2. Exposure estimates are expressed in terms of the mass of substance in contact with the body per unit body weight per unit time (e.g., mg chemical per kg body weight per day, also expressed as mg/kg-day). These exposure estimates are termed "intakes" (for the purposes of this manual) and represent the normalized exposure rate. Several terms common in other EPA documents and the literature are equivalent or related to intake (see box on this page and definitions box on page 6-2). Chemical intakes are calculated using equations that include variables for exposure concentration, contact rate, exposure frequency, exposure duration, body weight, and exposure averaging time. The values of some of these variables depend on site conditions and the characteristics of the potentially exposed population.

After intakes have been estimated, they are organized by population, as appropriate (Section 6.7). Then, the sources of uncertainty (e.g., variability in analytical data, modeling results, parameter assumptions) and their effect on the exposure estimates are evaluated and summarized (Section 6.8). This information on uncertainty is important to site decision-makers who must evaluate the results of the exposure and risk assessment and make decisions regarding the degree of remediation required at a site. The exposure assessment concludes with a summary of the estimated intakes for each pathway evaluated (Section 6.9).

TERMS EQUIVALENT OR RELATED TO INTAKE

Normalized Exposure Rate. Equivalent to intake

Administered Dose. Equivalent to intake

Applied Dose. Equivalent to intake

Absorbed Dose. Equivalent to intake multiplied by an absorption factor

6.1.2 REASONABLE MAXIMUM EXPOSURE

Actions at Superfund sites should be based on an estimate of the reasonable maximum exposure (RME) expected to occur under both current and future land-use conditions. The reasonable maximum exposure is defined here as the highest exposure that is reasonably expected to occur at a site. RMEs are estimated for individual pathways. If a population is exposed via more than one pathway, the combination of exposures across pathways also must represent an RME.

Estimates of the reasonable maximum exposure necessarily involve the use of professional judgment. This chapter provides guidance for determining the RME at a site and identifies some exposure variable values appropriate for use in this determination. The specific values identified should be regarded as general recommendations, and could change based on site-specific information and the particular needs of the EPA remedial project manager (RPM). Therefore, these recommendations should be used in conjunction with input from the RPM responsible for the site.

In the past, exposures generally were estimated for an average and an upper-bound exposure case, instead of a single exposure case (for both current and future land use) as recommended here. The advantage of the two case approach is that the resulting range of exposures provides some measure of the uncertainty surrounding these estimates. The disadvantage of this approach is that the upper-bound estimate of exposure may be above the range of possible exposures, whereas the average estimate is lower than exposures potentially experienced by much of the population. The intent of the RME is to estimate a conservative exposure case (i.e., well above the average case) that is still within the range of possible exposures. Uncertainty is still evaluated under this approach. However, instead of combining many sources of uncertainty into average and upper-bound exposure estimates, the variation in individual exposure variables is used to evaluate uncertainty (See Section 6.8). In this way, the variables contributing most to uncertainty in the exposure estimate are more easily identified.

6.2 STEP 1: CHARACTERIZATION OF EXPOSURE SETTING

The first step in evaluating exposure at Superfund sites is to characterize the site with respect to its physical characteristics as well as those of the human populations on and near the site. The output of this step is a qualitative evaluation of the site and surrounding populations with respect to those characteristics that influence exposure. All information gathered during this step will support the identification of exposure pathways in Step 2. In addition, the information on the potentially exposed populations will be used in Step 3 to determine the values of some intake variables.

6.2.1 CHARACTERIZE PHYSICAL SETTING

Characterize the exposure setting with respect to the general physical characteristics of the site. Important site characteristics include the following:

- climate (e.g., temperature, precipitation);
- meteorology (e.g., wind speed and direction);
- geologic setting (e.g., location and characterization of underlying strata);
- vegetation (e.g., unvegetated, forested, grassy);
- soil type (e.g., sandy, organic, acid, basic);
- ground-water hydrology (e.g., depth, direction and type of flow); and
- location and description of surface water (e.g., type, flow rates, salinity).

Sources of this information include site descriptions and data from the preliminary assessment (PA), site inspection (SI), and remedial investigation (RI) reports. Other sources include county soil surveys, wetlands maps, aerial photographs, and reports by the National Oceanographic and Atmospheric Association (NOAA) and the U.S. Geological Survey (USGS). The assessor also should consult with appropriate technical experts (e.g., hydrogeologists, air modelers) as needed to characterize the site.

6.2.2 CHARACTERIZE POTENTIALLY EXPOSED POPULATIONS

Characterize the populations on or near the site with respect to location relative to the site, activity patterns, and the presence of sensitive subgroups.

Determine location of current populations relative to the site . Determine the distance and direction of potentially exposed populations from the site. Identify those populations that are closest to or actually living on the site and that, therefore, may have the greatest potential for exposure. Be sure to include potentially exposed distant populations, such as public water supply consumers and distant consumers of fish or shellfish or agricultural products from the site area. Also include populations that could be exposed in the future to chemicals that have migrated from the site. Potential sources of this information include:

- site visit;
- other information gathered as part of the SI or during the initial stages of the RI;
- population surveys conducted near the site;
- topographic, land use, housing or other maps; and
- recreational and commercial fisheries data.

Determine current land use . Characterize the activities and activity patterns of the potentially exposed population. The following land use categories will be applicable most often at Superfund sites:

- residential;
- commercial/industrial; and
- recreational.

Determine the current land use or uses of the site and surrounding area. The best source of this information is a site visit. Look for homes, playgrounds, parks, businesses, industries, or other land uses on or in the vicinity of the site. Other sources on local land use include:

- zoning maps;
- state or local zoning or other land use-related laws and regulations;
- data from the U.S. Bureau of the Census;
- topographic, land use, housing or other maps; and
- aerial photographs.

Some land uses at a site may not fit neatly into one of the three land use categories and other land use classifications may be more appropriate (e.g., agricultural land use). At some sites it may be most appropriate to have more than one land use category.

After defining the land use(s) for a site, identify human activities and activity patterns associated with each land use. This is basically a "common sense" evaluation and is not based on any specific data sources, but rather on a general understanding of what activities occur in residential, business, or recreational areas.

Characterize activity patterns by doing the following.

- Determine the percent of time that the potentially exposed population(s) spend in the potentially contaminated area. For example, if the potentially exposed population is commercial or industrial, a reasonable maximum daily exposure period is likely to be 8 hours (a typical work day). Conversely, if the population is residential, a maximum daily exposure period of 24 hours is possible.
- Determine if activities occur primarily indoors, outdoors, or both. For example, office workers may spend all their time indoors, whereas construction workers may spend all their time outdoors.
- Determine how activities change with the seasons. For example, some outdoor, summertime recreational activities (e.g., swimming, fishing) will occur less frequently or not at all during the winter months. Similarly, children are likely to play outdoors less frequently and with more clothing during the winter months.
- Determine if the site itself may be used by local populations, particularly if access to the site is not restricted or otherwise limited (e.g., by distance). For example, children living in

the area could play onsite, and local residents could hunt or hike onsite.

- Identify any site-specific population characteristics that might influence exposure. For example, if the site is located near major commercial or recreational fisheries or shellfisheries, the potentially exposed population is likely to eat more locally-caught fish and shellfish than populations located inland.

Determine future land use. Determine if any activities associated with a current land use are likely to be different under an alternate future land use. For example, if ground water is not currently used in the area of the site as a source of drinking water but is of potable quality, future use of ground water as drinking water would be possible. Also determine if land use of the site itself could change in the future. For example, if a site is currently classified as industrial, determine if it could possibly be used for residential or recreational purposes in the future.

Because residential land use is most often associated with the greatest exposures, it is generally the most conservative choice to make when deciding what type of alternate land use may occur in the future. However, an assumption of future residential land use may not be justifiable if the probability that the site will support residential use in the future is exceedingly small.

Therefore, determine possible alternate future land uses based on available information and professional judgment. Evaluate pertinent information sources, including (as available):

- master plans (city or county projections of future land use);
- Bureau of the Census projections; and
- established land use trends in the general area and the area immediately surrounding the site (use Census Bureau or state or local reports, or use general historical accounts of the area).

Note that while these sources provide potentially useful information, they should not be interpreted as providing proof that a certain land use will or will not occur.

Assume future residential land use if it seems possible based on the evaluation of the available information. For example, if the site is currently industrial but is located near residential areas in an urban area, future residential land use may be a reasonable possibility. If the site is industrial and is located in a very rural area with a low population density and projected low growth, future residential use would probably be unlikely. In this case, a more likely alternate future land use may be recreational. At some sites, it may be most reasonable to assume that the land use will not change in the future.

There are no hard-and-fast rules by which to determine alternate future land use. The use of professional judgment in this step is critical. Be sure to consult with the RPM about any decision regarding alternate future land use. Support the selection of any alternate land use with a logical, reasonable argument in the exposure assessment chapter of the risk assessment report. Also include a qualitative statement of the likelihood of the future land use occurring.

Identify subpopulations of potential concern. Review information on the site area to determine if any subpopulations may be at increased risk from chemical exposures due to increased sensitivity, behavior patterns that may result in high exposure, and/or current or past exposures from other sources. Subpopulations that may be more sensitive to chemical exposures include infants and children, elderly people, pregnant and nursing women, and people with chronic illnesses. Those potentially at higher risk due to behavior patterns include children, who are more likely to contact soil, and persons who may eat large amounts of locally caught fish or locally grown produce (e.g., home-grown vegetables). Subpopulations at higher risk due to exposures from other sources include individuals exposed to chemicals during occupational activities and individuals living in industrial areas.

To identify subpopulations of potential concern in the site area, determine locations of schools, day care centers, hospitals, nursing homes, retirement communities, residential areas with children, important commercial or recreational fisheries near the site, and major industries potentially involving chemical exposures. Use local census data and information from local public health officials for this determination.

6.3 STEP 2: IDENTIFICATION OF EXPOSURE PATHWAYS

This section describes an approach for identifying potential human exposure pathways at a Superfund site. An exposure pathway describes the course a chemical or physical agent takes from the source to the exposed individual. An exposure pathway analysis links the sources, locations, and types of environmental releases with population locations and activity patterns to determine the significant pathways of human exposure.

An exposure pathway generally consists of four elements: (1) a source and mechanism of chemical release, (2) a retention or transport medium (or media in cases involving media transfer of chemicals), (3) a point of potential human contact with the contaminated medium (referred to as the exposure point), and (4) an exposure route (e.g., ingestion) at the contact point. A medium contaminated as a result of a past release can be a contaminant source for other media (e.g., soil contaminated from a previous spill could be a contaminant source for ground water or surface water). In some cases, the source itself (i.e., a tank, contaminated soil) is the exposure point, without a release to any other medium. In these latter cases, an exposure pathway consists of (1) a source, (2) an exposure point, and (3) an exposure route. Exhibit 6-2 illustrates the basic elements of each type of exposure pathway.

The following sections describe the basic analytical process for identifying exposure pathways at Superfund sites and for selecting pathways for quantitative analysis. The pathway analysis described below is meant to be a qualitative evaluation of pertinent site and chemical information, and not a rigorous quantitative evaluation of factors such as source strength, release rates, and chemical fate and transport. Such factors are considered later in the exposure assessment during the quantitative determination of exposure concentrations (Section 6.5).

6.3.1 IDENTIFY SOURCES AND RECEIVING MEDIA

To determine possible release sources for a site in the absence of remedial action, use all available site descriptions and data from the PA, SI, and RI reports. Identify potential release mechanisms and receiving media for past, current, and future releases. Exhibit 6-3 lists some typical release sources, release mechanisms, and receiving media at Superfund sites. Use monitoring data in conjunction with information on source locations to support the analysis of past, continuing, or threatened releases. For example, soil contamination near an old tank would suggest the tank (source) ruptured or leaked (release mechanism) to the ground (receiving media). Be sure to note any source that could be an exposure point in addition to a release source (e.g., open barrels or tanks, surface waste piles or lagoons, contaminated soil).

Map the suspected source areas and the extent of contamination using the available information and monitoring data. As an aid in evaluating air sources and releases, Volumes I and II of the National Technical Guidance Studies (NTGS; EPA 1989a,b) should be consulted.

EXHIBIT 6-2
ILLUSTRATION OF EXPOSURE PATHWAYS

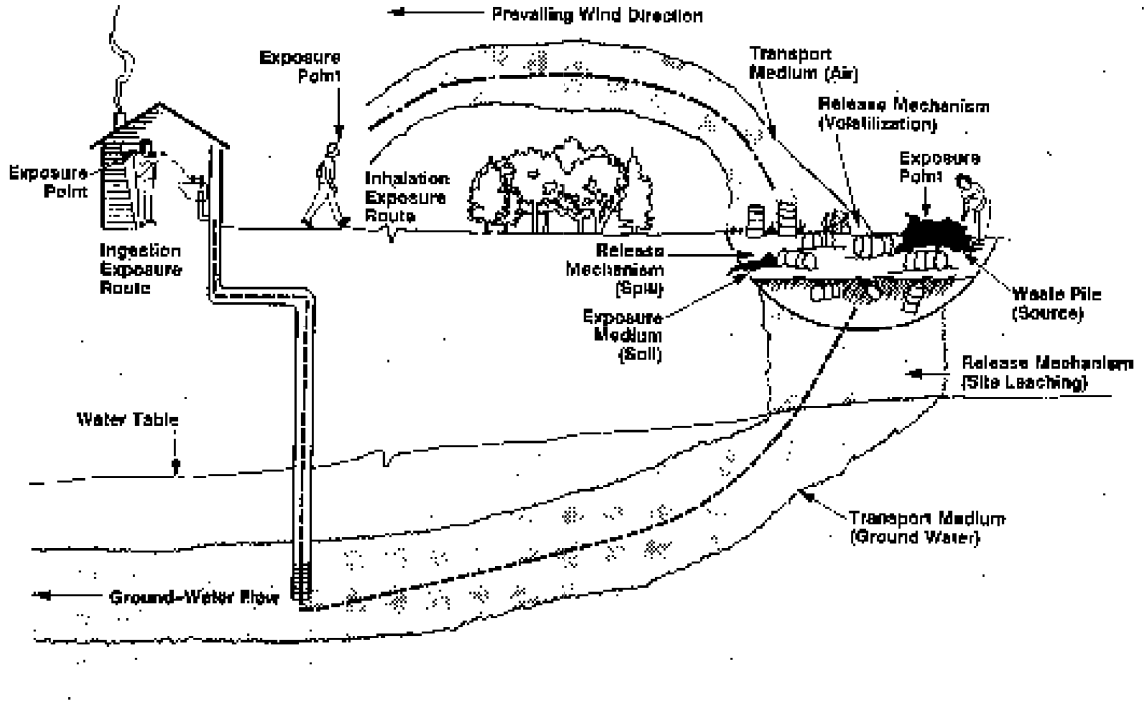


EXHIBIT 6-3

COMMON CHEMICAL RELEASE SOURCES AT SITES IN THE ABSENCE OF REMEDIAL ACTION

Receiving Medium	Release Mechanism	Release Source
Air	Volatilization	Surface wastes -- lagoons, ponds, pits, spills Contaminated surface water Contaminated surface soil Contaminated wetlands Leaking drums
	Fugitive dust generation	Contaminated surface soil Waste piles
Surface water	Surface runoff	Contaminated surface soil
	Episodic overland flow	Lagoon overflow Spills, leaking containers
	Ground-water seepage	Contaminated ground water
Ground water	Leaching	Surface or buried wastes Contaminated soil
Soil	Leaching	Surface or buried wastes
	Surface runoff	Contaminated surface soil
	Episodic overland flow	Lagoon overflow Spills, leaking containers
	Fugitive dust generation/ deposition	Contaminated surface soil Waste piles
	Tracking	Contaminated surface soil
Sediment	Surface runoff, Episodic overland flow	Surface wastes -- lagoons, ponds, pits, spills Contaminated surface soil
	Ground-water seepage	Contaminated ground water
	Leaching	Surface or buried wastes Contaminated soil
Biota	Uptake (direct contact, ingestion, inhalation)	Contaminated soil, surface water, sediment, ground water or air Other biota

6.3.2 EVALUATE FATE AND TRANSPORT IN RELEASE MEDIA

Evaluate the fate and transport of the chemicals to predict future exposures and to help link sources with currently contaminated media. The fate and transport analysis conducted at this stage of the exposure assessment is not meant to result in a quantitative evaluation of media-specific chemical concentrations. Rather, the intent is to identify media that are receiving or may receive site-related chemicals. At this stage, the assessor should answer the questions: What chemicals occur in the sources at the site and in the environment? In what media (onsite and offsite) do they occur now? In what media and at what location may they occur in the future? Screening-level analyses using available data and simplified calculations or analytical models may assist in this qualitative evaluation.

After a chemical is released to the environment it may be:

- transported (e.g., convected downstream in water or on suspended sediment or through the atmosphere);
- physically transformed (e.g., volatilization, precipitation);
- chemically transformed (e.g., photolysis, hydrolysis, oxidation, reduction, etc.);
- biologically transformed (e.g, biodegradation); and/or
- accumulated in one or more media (including the receiving medium).

To determine the fate of the chemicals of potential concern at a particular site, obtain information on their physical/chemical and environmental fate properties. Use computer data bases (e.g., SRC's Environmental Fate, CHEMFATE, and BIODEG data bases; BIOSIS; AQUIRE) and the open literature as necessary as sources for up-to-date information on the physical/chemical and fate properties of the chemicals of potential concern. Exhibit 6-4 lists some important chemical-specific fate parameters and briefly describes how these can be used to evaluate a chemical's environmental fate.

Also consider site-specific characteristics (identified in Section 6.2.1) that may influence fate and transport. For example, soil characteristics such as moisture content, organic carbon content, and cation exchange capacity can greatly influence the movement of many chemicals. A high water table may increase the probability of leaching of chemicals in soil to ground water.

Use all applicable chemical and site-specific information to evaluate transport within and between media and retention or accumulation within a single medium. Use monitoring data to identify media that are contaminated now and the fate pathway analysis to identify media that may be contaminated now (for media not sampled) or in the future. Exhibit 6-5 presents some important questions to consider when developing these pathways. Exhibit 6-6 presents a series of flow charts useful when evaluating the fate and transport of chemicals at a site.

6.3.3 IDENTIFY EXPOSURE POINTS AND EXPOSURE ROUTES

After contaminated or potentially contaminated media have been identified, identify exposure points by determining if and where any of the potentially exposed populations (identified in Step 1) can contact these media. Consider population locations and activity patterns in the area, including those of subgroups that may be of particular concern. Any point of potential contact with a contaminated medium is an exposure point. Try to identify those exposure points where the concentration that will be contacted is the greatest. Therefore, consider including any contaminated media or sources onsite as a potential exposure point if the site is currently used, if access to the site under current conditions is not restricted or otherwise limited (e.g., by distance), or if contact is possible under an alternate future land use. For potential offsite exposures, the highest exposure concentrations often will be at the points closest to and downgradient or downwind of the site. In some cases, highest concentrations may be encountered at points distant from the site. For example, site-related chemicals may be transported and deposited in a distant water body where they may be subsequently bioconcentrated by aquatic organisms.

EXHIBIT 6-4

IMPORTANT PHYSICAL/CHEMICAL AND ENVIRONMENTAL FATE PARAMETERS

K_{oc} provides a measure of the extent of chemical partitioning between organic carbon and water at equilibrium. The higher the K_{oc}, the more likely a chemical is to bind to soil or sediment than to remain in water.

K_d provides a soil or sediment-specific measure of the extent of chemical partitioning between soil or sediment and water, unadjusted for dependence upon organic carbon. To adjust for the fraction of organic carbon present in soil or sediment (f_{oc}), use $K_d = K_{oc} \times f_{oc}$. The higher the K_d, the more likely a chemical is to bind to soil or sediment than to remain in water.

K_{ow} provides a measure of the extent of chemical partitioning between water and octanol at equilibrium. The greater the K_{ow} the more likely a chemical is to partition to octanol than to remain in water. Octanol is used as a surrogate for lipids (fat), and K_{ow} can be used to predict bioconcentration in aquatic organisms.

Solubility is an upper limit on a chemical's dissolved concentration in water at a specified temperature. Aqueous concentrations in excess of solubility may indicate sorption onto sediments, the presence of solubilizing chemicals such as solvents, or the presence of a non-aqueous phase liquid.

Henry's Law Constant provides a measure of the extent of chemical partitioning between air and water at equilibrium. The higher the Henry's Law constant, the more likely a chemical is to volatize than to remain in water.

Vapor Pressure is the pressure exerted by a chemical vapor in equilibrium with its solid or liquid form at any given temperature. It is used to calculate the rate of volatilization of a pure substance from a surface or in estimating a Henry's Law constant for chemicals with low water solubility. The higher the vapor pressure, the more likely a chemical is to exist in a gaseous state.

Diffusivity describes the movement of a molecule in a liquid or gas medium as a result of differences in concentration. It is used to calculate the dispersive component of chemical transport. The higher the diffusivity, the more likely a chemical is to move in response to concentration gradients.

Bioconcentration Factor (BCF) provides a measure of the extent of chemical partitioning at equilibrium between a biological medium such as fish tissue or plant tissue and an external medium such as water. The higher the BCF, the greater the accumulation in living tissue is likely to be.

Media-specific Half-life provides a relative measure of the persistence of a chemical in a given medium, although actual values can vary greatly depending on site-specific conditions. The greater the half-life, the more persistent a chemical is likely to be.

EXHIBIT 6-5

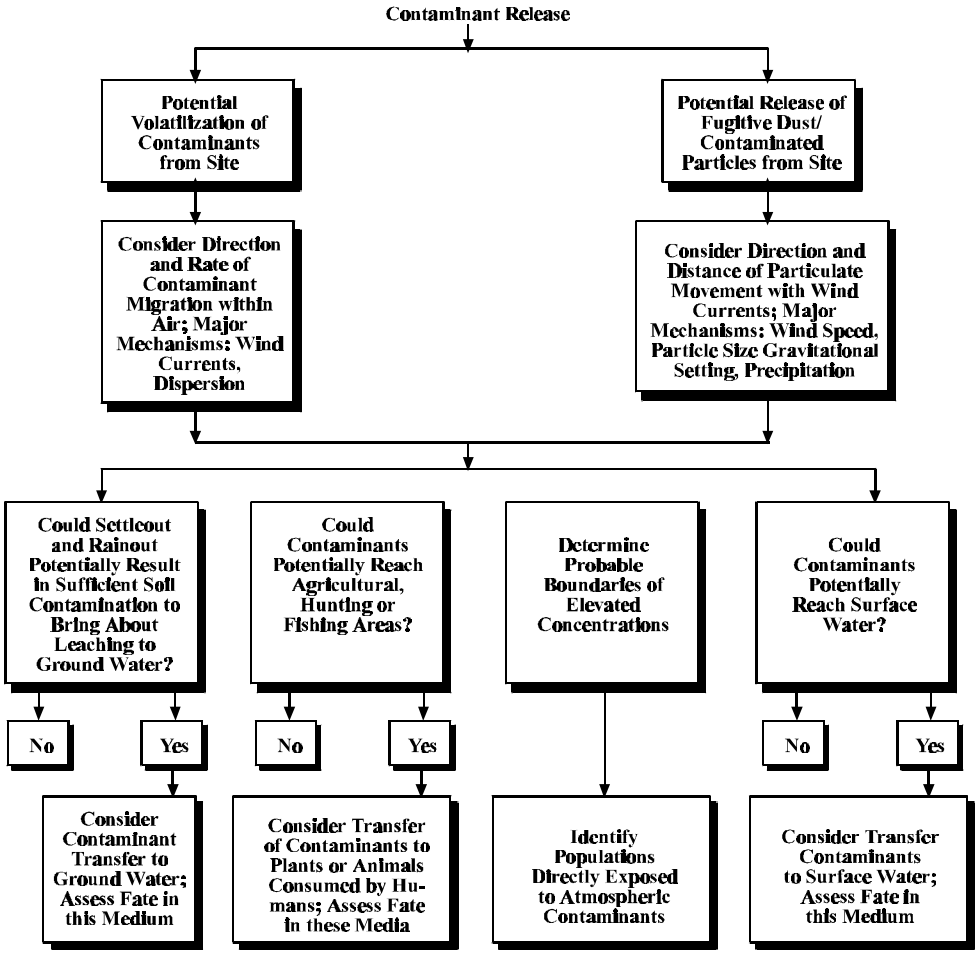
IMPORTANT CONSIDERATIONS FOR DETERMINING THE ENVIRONMENTAL FATE AND TRANSPORT OF THE CHEMICALS OF POTENTIAL CONCERN AT A SUPERFUND SITE

- **What are the principal mechanisms for change or removal in each of the environmental media?**
- **How does the chemical behave in air, water, soil, and biological media? Does it bioaccumulate or biodegrade? Is it absorbed or taken up by plants?**
- **Does the agent react with other compounds in the environment?**
- **Is there intermedia transfer? What are the mechanisms for intermedia transfer? What are the rates of the intermedia transfer or reaction mechanism?**
- **How long might the chemical remain in each environmental medium? How does its concentration change with time in each medium?**
- **What are the products into which the agent might degrade or change in the environment? Are these products potentially of concern?**
- **Is a steady-state concentration distribution in the environment or in specific segments of the environment achieved?**

EXHIBIT 6-6

FLOW CHART FOR FATE AND TRANSPORT ASSESSMENTS

Environmental fate and transport assessment: atmosphere



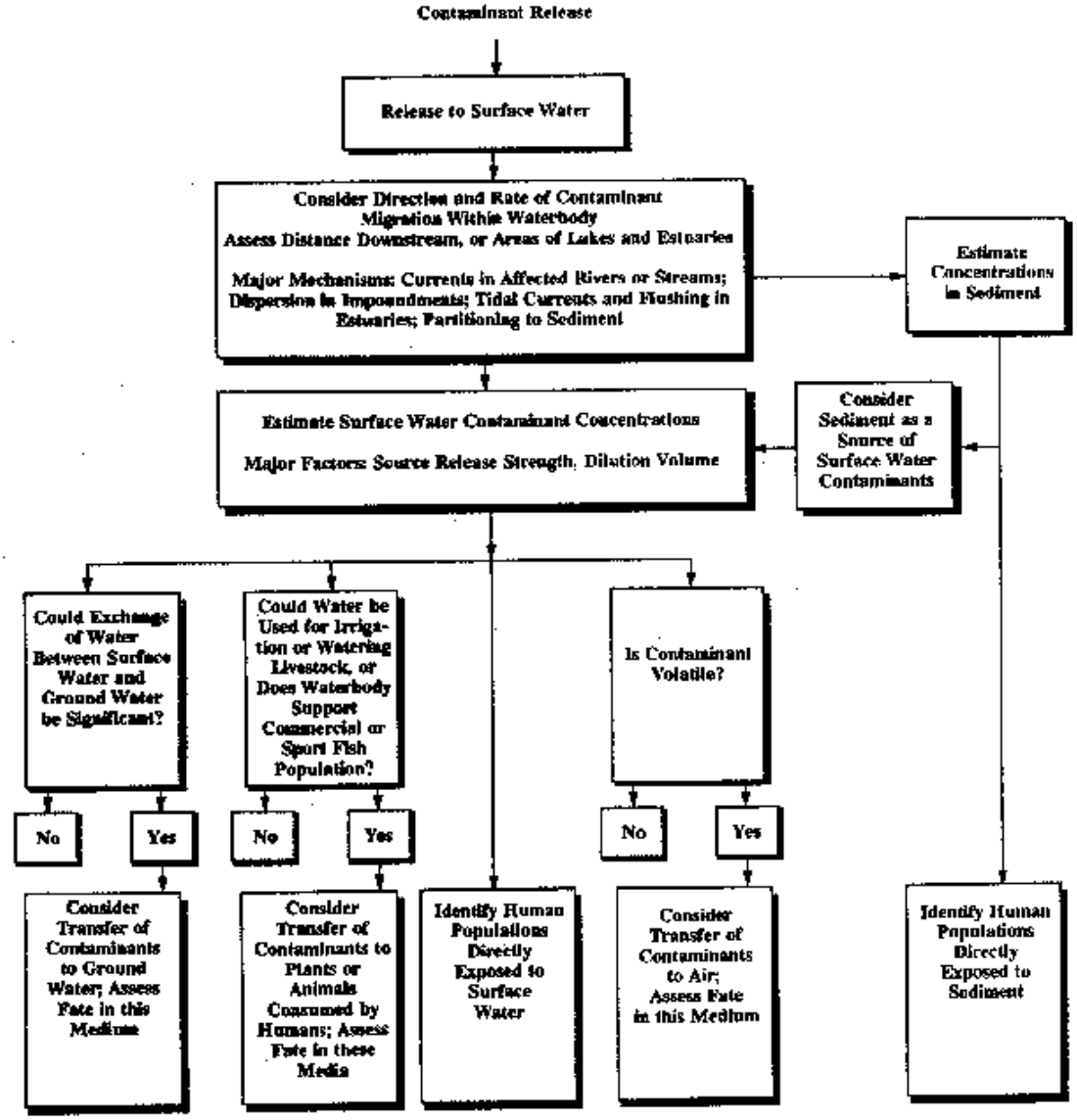
Source: Adapted from EPA 1988b

(continued)

EXHIBIT 6–6 (continued)

FLOW CHART FOR FATE AND TRANSPORT ASSESSMENTS

Environmental fate and transport assessment: surface water and sediment



Source: Adapted from EPA 1988b.

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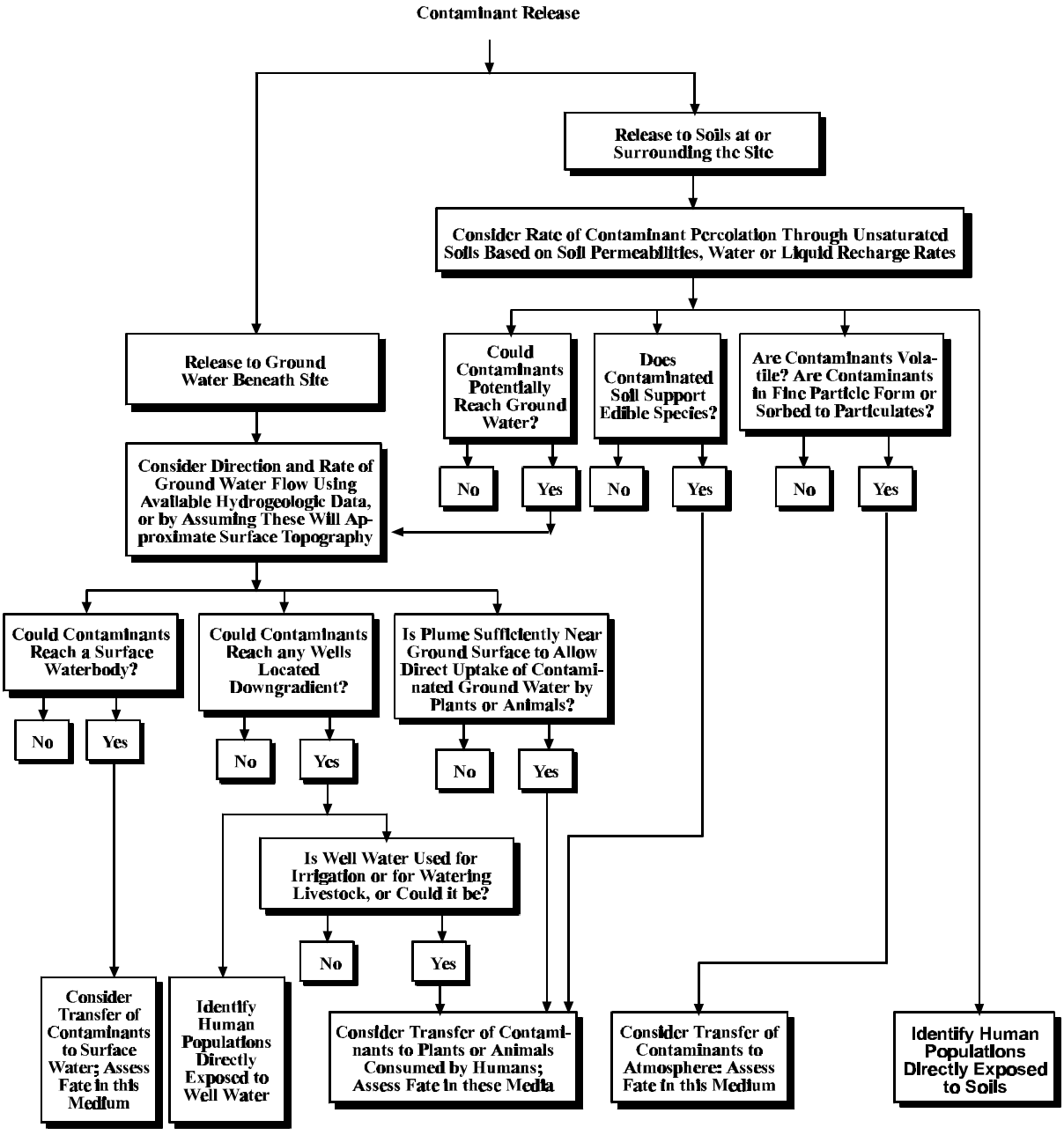
EXHIBIT 6-6 (continued)

FLOW CHART FOR FATE AND TRANSPORT ASSESSMENTS

Environmental fate and transport assessment: soils and ground water



Source: Adapted from EPA 1988b

After determining exposure points, identify probable exposure routes (i.e., ingestion, inhalation, dermal contact) based on the media contaminated and the anticipated activities at the exposure points. In some instances, an exposure point may exist but an exposure route may not (e.g., a person touches contaminated soil but is wearing gloves). Exhibit 6-7 presents a population/exposure route matrix that can be used in determining potential exposure routes at a site.

6.3.4 INTEGRATE INFORMATION ON SOURCES, RELEASES, FATE AND TRANSPORT, EXPOSURE POINTS, AND EXPOSURE ROUTES INTO EXPOSURE PATHWAYS

Assemble the information developed in the previous three steps and determine the complete exposure pathways that exist for the site. A pathway is complete if there is (1) a source or chemical release from a source, (2) an exposure point where contact can occur, and (3) an exposure route by which contact can occur. Otherwise, the pathway is incomplete, such as the situation where there is a source releasing to air but there are no nearby people. If available from ATSDR, human monitoring data indicating chemical accumulation or chemical-related effects in the site area can be used as evidence to support conclusions about which exposure pathways are complete; however, negative data from such studies should not be used to conclude that a pathway is incomplete.

From all complete exposure pathways at a site, select those pathways that will be evaluated further in the exposure assessment. If exposure to a sensitive subpopulation is possible, select that pathway for quantitative evaluation. All pathways should be selected for further evaluation unless there is sound justification (e.g., based on the results of a screening analysis) to eliminate a pathway from detailed analysis. Such a justification could be based on one of the following:

- the exposure resulting from the pathway is much less than that from another pathway involving the same medium at the same exposure point;
- the potential magnitude of exposure from a pathway is low; or
- the probability of the exposure occurring is very low and the risks associated with the occurrence are not high (if a pathway has catastrophic consequences, it should be selected for evaluation even if its probability of occurrence is very low).

Use professional judgment and experience to make these decisions. Before deciding to exclude a pathway from quantitative analysis, consult with the RPM. If a pathway is excluded from further analysis, clearly document the reasons for the decision in the exposure assessment section of the risk assessment report.

For some complete pathways it may not be possible to quantify exposures in the subsequent steps of the analysis because of a lack of data on which to base estimates of chemical release, environmental concentration, or human intake. Available modeling results should complement and supplement the available monitoring data to minimize such problems. However, uncertainties associated with the modeling results may be too large to justify quantitative exposure assessment in the absence of monitoring data to validate the modeling results. These pathways should nevertheless be carried through the exposure assessment so that risks can be qualitatively evaluated or so that this information can be considered during the uncertainty analysis of the results of the exposure assessment (see Section 6.8) and the risk assessment (see Chapter 8).

6.3.5 SUMMARIZE INFORMATION ON ALL COMPLETE EXPOSURE PATHWAYS

Summarize pertinent information on all complete exposure pathways at the site by identifying potentially exposed populations, exposure media, exposure points, and exposure routes. Also note if the pathway has been selected for quantitative evaluation; summarize the justification if a pathway has been excluded. Summarize pathways for current land use and any alternate future land use separately. This summary information is useful for defining the scope of the next step (quantification of exposure) and also is useful as documentation of the exposure pathway analysis. Exhibit 6-8 provides a sample format for presenting this information.

EXHIBIT 6-7
MATRIX OF POTENTIAL EXPOSURE ROUTES

Exposure Medium/ Exposure Route	Residential Population	Commercial/Industrial Population	Recreational Population
Ground Water			
Ingestion	L	A	--
Dermal Contact	L	A	--
Surface Water			
Ingestion	L	A	L,C
Dermal Contact	L	A	L,C
Sediment			
Incidental Ingestion	C	A	C
Dermal Contact	C	A	L,C
Air			
Inhalation of Vapor Phase Chemicals			
Indoors	L	A	--
Outdoors	L	A	L
Inhalation of Particulates			
Indoors	L	A	--
Outdoors	L	A	L
Soil/Dust			
Incidental Ingestion	L,C	A	L,C
Dermal Contact	L,C	A	L,C
Food			
Ingestion			
Fish and Shellfish	L	–	L
Meat and Game	L	–	L
Dairy	L,C	–	L
Eggs	L	–	L
Vegetables	L	–	L

L = lifetime exposure
C = exposure in children may be significantly greater than in adults
A = exposure to adults (highest exposure is likely to occur during occupational activities)

-- = Exposure of this population via this route is not likely to occur.

6.4 STEP 3: QUANTIFICATION OF EXPOSURE: GENERAL CONSIDERATIONS

The next step in the exposure assessment process is to quantify the magnitude, frequency and duration of exposure for the populations and exposure pathways selected for quantitative evaluation. This step is most often conducted in two stages: first, exposure concentrations are estimated, then, pathway-specific intakes are quantified. The specific methodology for calculating exposure concentrations and pathway-specific exposures are presented in Sections 6.5 and 6.6, respectively. This section describes some of the basic concepts behind these processes.

6.4.1 QUANTIFYING THE REASONABLE MAXIMUM EXPOSURE

Exposure is defined as the contact of an organism with a chemical or physical agent. If exposure occurs over time, the total exposure can be divided by a time period of interest to obtain an average exposure rate per unit time. This average exposure rate also can be expressed as a function of body weight. For the purposes of this manual, exposure normalized for time and body weight is termed "intake", and is expressed in units of mg chemical/kg body weight-day.

Exhibit 6-9 presents a generic equation for calculating chemical intakes and defines the intake variables. There are three categories of variables that are used to estimate intake:

(1) chemical-related variable -- exposure concentration;

(2) variables that describe the exposed population -- contact rate, exposure frequency and duration, and body weight; and

(3) assessment-determined variable -- averaging time.

Each intake variable in the equation has a range of values. For Superfund exposure assessments, intake variable values for a given pathway should be selected so that the combination of all intake variables results in an estimate of the reasonable maximum exposure for that pathway. As defined previously, the reasonable maximum exposure (RME) is the maximum exposure that is reasonably expected to occur at a site. Under this approach, some intake variables may not be at their individual maximum values but when in combination with other variables will result in estimates of the RME. Some recommendations for determining the values of the individual intake variables are discussed below. These recommendations are based on EPA's determination of what would result in an estimate of the RME. As discussed previously, a determination of "reasonable" cannot be based solely on quantitative information, but also requires the use of professional judgment. Accordingly, the recommendations below are based on a combination of quantitative information and professional judgment. These are general recommendations, however, and could change based on site-specific information or the particular needs of the risk manager. Consult with the RPM before varying from these recommendations.

Exposure concentration. The concentration term in the intake equation is the arithmetic average of the concentration that is contacted over the exposure period. Although this concentration does not reflect the maximum concentration that could be contacted at any one time, it is regarded as a reasonable estimate of the concentration likely to be contacted over time. This is because in most situations, assuming long-term contact with the maximum concentration is not reasonable. (For exceptions to this generalization, see discussion of hot spots in Section 6.5.3.)

Because of the uncertainty associated with any estimate of exposure concentration, the upper confidence limit (i.e., the 95 percent upper confidence limit) on the arithmetic average will be used for this variable. There are standard statistical methods which can be used to calculate the upper confidence limit on the arithmetic mean. Gilbert (1987, particularly sections 11.6 and 13.2) discusses methods that can be applied to data that are distributed normally or log normally. Kriging is another method that potentially can be used (Clark 1979 is one of several reference books on kriging). A statistician should be consulted for more details or for assistance with specific methods.

EXHIBIT 6-8

EXAMPLE OF TABLE FORMAT FOR SUMMARIZING COMPLETE EXPOSURE PATHWAYS AT A SITE

Potentially Exposed Population	Exposure Route, Medium and Exposure Point	Pathway Selected for Evaluation?	Reason for Selection or Exclusion
Current Land Use			
Residents	Ingestion of ground water from local wells down-gradient of the site	Yes	Residents use ground water from local wells as drinking water.
Residents	Inhalation of chemicals volatilized from ground water during home use	Yes	Some of the chemicals of potential concern in ground water are volatile, and ground water is used by local residents.
Industrial Workers	Direct contact with chemicals of potential concern in soil on the site	Yes	Contaminated soil is in an area potentially used by outside maintenance workers.
Future Land Use			
Residents	Direct contact with chemicals of potential concern in soil on the site	Yes	Area could be developed in the future as a residential area.
Residents	Ingestion of chemicals that have accumulated in fish located in onsite ponds	No	The potential for significant exposure via this pathway is low because none of the chemicals of potential concern accumulate extensively in fish.

EXHIBIT 6-9

GENERIC EQUATION FOR CALCULATING CHEMICAL INTAKES

$$I = C \times CR \times EFD \times \frac{1}{BW} \times \frac{1}{AT}$$

Where:

I = intake; the amount of chemical at the exchange boundary (mg/kg body weight-day)

Chemical-related variable

C = chemical concentration; the average concentration contacted over the exposure period (e.g., mg/liter water)

Variables that describe the exposed population

CR = contact rate; the amount of contaminated medium contacted per unit tine or event (e.g., liters/day)

EFD = exposure frequency and duration; describes how long and how often exposure occurs. Often calculated using two terms (EF and ED):

EF = exposure frequency (days/year)

ED = exposure duration (years)

BW = body weight; the average body weight over the exposure period (kg)

Assessment-determined variable

AT = averaging time; period over which exposure is averaged (days)

If there is great variability in measured or modeled concentration values (such as when too few samples are taken or when model inputs are uncertain), the upper confidence limit on the average concentration will be high, and conceivably could be above the maximum detected or modeled value. In these cases, the maximum detected or modeled value should be used to estimate exposure concentrations. This could be regarded by some as too conservative an estimate, but given the uncertainty in the data in these situations, this approach is regarded as reasonable.

For some sites, where a screening level analysis is regarded as sufficient to characterize potential exposures, calculation of the upper confidence limit on the arithmetic average is not required. In these cases, the maximum detected or modeled concentration should be used as the exposure concentration.

Contact rate. Contact rate reflects the amount of contaminated medium contacted per unit time or event. If statistical data are available for a contact rate, use the 95th percentile value for this variable. (In this case and throughout this chapter, the 90th percentile value can be used if the 95th percentile value is not available.) If statistical data are not available, professional judgment should be used to estimate a value which approximates the 95th percentile value. (It is recognized that such estimates will not be precise. They should, however, reflect a reasonable estimate of an upper-bound value.)

Sometimes several separate terms are used to derive an estimate of contact rate. For example, for dermal contact with chemicals in water, contact rate is estimated by combining information on exposed skin surface area, dermal permeability of a chemical, and exposure time. In such instances, the combination of variables used to estimate intake should result in an estimate approximating the 95th percentile value. Professional judgment will be needed to determine the appropriate combinations of variables. (More specific guidance for determining contact rate for various pathways is given in Section 6.6.)

Exposure frequency and duration. Exposure frequency and duration are used to estimate the total time of exposure. These terms are determined on a site-specific basis. If statistical data are available, use the 95th percentile value for exposure time. In the absence of statistical data (which is usually the case), use reasonable conservative estimates of exposure time. National statistics are available on the upper-bound (90th percentile) and average (50th percentile) number of years spent by individuals at one residence (EPA 1989d). Because of the data on which they are based, these values may underestimate the actual time that someone might live in one residence. Nevertheless, the upper-bound value of 30 years can be used for exposure duration when calculating reasonable maximum residential exposures. In some cases, however, lifetime exposure (70 years by convention) may be a more appropriate assumption. Consult with the RPM regarding the appropriate exposure duration for residential exposures. The exposure frequency and duration selected must be appropriate for the contact rate selected. If a long-term average contact rate (e.g., daily fish ingestion rate averaged over a year) is used, then a daily exposure frequency (i.e., 365 days/year) should be assumed.

Body weight. The value for body weight is the average body weight over the exposure period. If exposure occurs only during childhood years, the average child body weight during the exposure period should be used to estimate intake. For some pathways, such as soil ingestion, exposure can occur throughout the lifetime but the majority of exposure occurs during childhood (because of higher contact rates). In these cases, exposures should be calculated separately for age groups with similar contact rate to body weight ratios; the body weight used in the intake calculation for each age group is the average body weight for that age group. Lifetime exposure is then calculated by taking the time-weighted average of exposure estimates over all age groups. For pathways where contact rate to body weight ratios are fairly constant over a lifetime (e.g., drinking water ingestion), a body weight of 70 kg is used.

A constant body weight over the period of exposure is used primarily by convention, but also because body weight is not always independent of the other variables in the exposure equation (most notably, intake). By keeping body weight constant, error from this dependence is minimized. The average body weight is used because, when combined with the other variable values in the intake equation, it is believed to result in the best estimate of the RME. For example, combining a 95th percentile contact rate with a 5th percentile body weight is not considered reasonable because it is unlikely that smallest person would have the highest intake. Alternatively, combining a 95th percentile intake with a 95th percentile body weight is not considered a maximum because a smaller person could have a higher contact rate to body weight ratio.

Averaging time. The averaging time selected depends on the type of toxic effect being assessed. When evaluating exposures to developmental toxicants, intakes are calculated by averaging over the exposure event (e.g., a day or a single exposure incident). For acute toxicants, intakes are calculated by averaging over the shortest exposure period that could produce an effect, usually an exposure event or a day. When evaluating longer-term exposure to noncarcinogenic toxicants, intakes are calculated by averaging intakes over the period of exposure (i.e., subchronic or chronic daily intakes). For carcinogens, intakes are calculated by prorating the total cumulative dose over a lifetime (i.e., chronic daily intakes, also called lifetime average daily intake). This distinction relates to the currently held scientific opinion that the mechanism of action for each category is different (see Chapter 7 for a discussion). The approach for carcinogens is based on the assumption that a high dose received over a short period of time is equivalent to a corresponding low dose spread over a lifetime (EPA 1986b). This approach becomes problematic as the exposures in question become more intense but less frequent, especially when there is evidence that the agent has shown dose-rate related carcinogenic effects. In some cases, therefore, it may be necessary to consult a toxicologist to assess the level of uncertainty associated with the exposure assessment for carcinogens. The discussion of uncertainty should be included in both the exposure assessment and risk characterization chapters of the risk assessment report.

6.4.2 TIMING CONSIDERATIONS

At many Superfund sites, long-term exposure to relatively low chemical concentrations (i.e., chronic daily intakes) are of greatest concern. In some situations, however, shorter-term exposures (e.g., subchronic daily intakes) also may be important. When deciding whether to evaluate short-term exposure, the following factors should be considered:

- the toxicological characteristics of the chemicals of potential concern;
- the occurrence of high chemical concentrations or the potential for a large release;
- persistence of the chemical in the environment; and
- the characteristics of the population that influence the duration of exposure.

Toxicity considerations. Some chemicals can produce an effect after a single or very short-term exposure to relatively low concentrations. These chemicals include acute toxicants such as skin irritants and neurological poisons, and developmental toxicants. At sites where these types of chemicals are present, it is important to assess exposure for the shortest time period that could result in an effect. For acute toxicants this is usually a single exposure event or a day, although multiple exposures over several days also could result in an effect. For developmental toxicants, the time period of concern is the exposure event. This is based on the assumption that a single exposure at the critical time in development is sufficient to produce an adverse effect. It should be noted that the critical time referred to can occur in almost any segment of the human population (i.e., fertile men and women, the conceptus, and the child up to the age of sexual maturation [EPA 1989e]).

Concentration considerations. Many chemicals can produce an effect after a single or very short-term exposure, but only if exposure is to a relatively high concentration. Therefore, it is important that the assessor identify possible situations where a short-term exposure to a high concentration could occur. Examples of such a situation include sites where contact with a small, but highly contaminated area is possible (e.g., a source or a hot spot), or sites where there is a potential for a large chemical release (e.g., explosions, ruptured drums, breached lagoon dikes). Exposure should be determined

for the shortest period of time that could produce an effect.

Persistence considerations. Some chemicals may degrade rapidly in the environment. In these cases, exposures should be assessed only for that period of time in which the chemical will be present at the site. Exposure assessments in these situations may need to include evaluations of exposure to the breakdown products, if they are persistent or toxic at the levels predicted to occur at the site.

Population considerations. At some sites, population activities are such that exposure would occur only for a short time period (a few weeks or months), infrequently, or intermittently. Examples of this would be seasonal exposures such as during vacations or other recreational activities. The period of time over which exposures are averaged in these instances depends on the type of toxic effect being assessed (see previous discussion on averaging time, Section 6.4.1).

6.5 QUANTIFICATION OF EXPOSURE: DETERMINATION OF EXPOSURE CONCENTRATIONS

This section describes the basic approaches and methodology for determining exposure concentrations of the chemicals of potential concern in different environmental media using available monitoring data and appropriate models. As discussed in Section 6.4.1, the concentration term in the exposure equation is the average concentration contacted at the exposure point or points over the exposure period. When estimating exposure concentrations, the objective is to provide a conservative estimate of this average concentration (e.g., the 95 percent upper confidence limit on the arithmetic mean chemical concentration).

This section provides an overview of the basic concepts and approaches for estimating exposure concentrations. It identifies what type of information is needed to estimate concentrations, where to find it, and how to interpret and use it. This section is not designed to provide all the information necessary to derive exposure concentrations and, therefore, does not detail the specifics of potentially applicable models nor provide the data necessary to run the models or support concentration estimates. However, sources of such information, including the *Superfund Exposure Assessment Manual* (SEAM; EPA 1988b) are referenced throughout the discussion.

6.5.1 GENERAL CONSIDERATIONS FOR ESTIMATING EXPOSURE CONCENTRATIONS

In general, a great deal of professional judgment is required to estimate exposure concentrations. Exposure concentrations may be estimated by (1) using monitoring data alone, or (2) using a combination of monitoring data and environmental fate and transport models. In most exposure assessments, some combination of monitoring data and environmental modeling will be required to estimate exposure concentrations.

Direct use of monitoring data . Use of monitoring data to estimate exposure concentrations is normally applicable where exposure involves direct contact with the monitored medium (e.g., direct contact with chemicals in soil or sediment), or in cases where monitoring has occurred directly at an exposure point (e.g., a residential drinking water well or public water supply). For these exposure pathways, monitoring data generally provide the best estimate of current exposure concentrations.

As the first step in estimating exposure concentrations, summarize available monitoring data. The manner in which the data are summarized depends upon the site characteristics and the pathways being evaluated. It may be necessary to divide chemical data from a particular medium into subgroups based on the location of sample points and the potential exposure pathways. In other instances, as when the sampling point is an exposure point (e.g., when the sample is from an existing drinking water well) it may not be appropriate to group samples at all, but may be most appropriate to treat the sample data separately when estimating intakes. Still,

in other instances, the assessor may wish to use the maximum concentration from a medium as the exposure concentration for a given pathway as a screening approach to place an upper bound on exposure. In these cases it is important to remember that if a screening level approach suggests a potential health concern, the estimates of exposure should be modified to reflect more probable exposure conditions.

In those instances where it is appropriate to group sampling data from a particular medium, calculate for each exposure medium and each chemical the 95 percent upper confidence limit on the arithmetic average chemical concentration. See Chapter 5 for guidance on how to treat sample concentrations below the quantitation limit.

Modeling approaches . In some instances, it may not be appropriate to use monitoring data alone, and fate and transport models may be required to estimate exposure concentrations. Specific instances where monitoring data alone may not be adequate are as follows.

- Where exposure points are spatially separate from monitoring points. Models may be required when exposure points are remote from sources of contamination if mechanisms for release and transport to exposure points exist (e.g., ground-water transport, air dispersion).

- Where temporal distribution of data is lacking. Typically, data from Superfund investigations are collected over a relatively short period of time. This generally will give a clear indication of current site conditions, but both long-term and short-term exposure estimates usually are required in Superfund exposure assessments. Although there may be situations where it is reasonable to assume that concentrations will remain constant over a long period of time, in many cases the time span of the monitoring data is not adequate to predict future exposure concentrations. Environmental models may be required to make these predictions.

- Where monitoring data are restricted by the limit of quantitation. Environmental models may be needed to predict concentrations of contaminants that may be present at concentrations that are below the quantitation limit but that may still cause toxic effects (even at such low concentrations). For example, in the case of a ground-water plume discharging into a river, the dilution afforded by the river may be sufficient to reduce the concentration of the chemical to a level that could not be detected by direct monitoring. However, as discussed in Section 5.3.1, the chemical may be sufficiently toxic or bioaccumulative that it could present a health risk at concentrations below the limit of quantitation. Models may be required to make exposure estimates in these types of situations.

A wide variety of models are available for use in exposure assessments. SEAM (EPA 1988b) and the *Exposure Assessment Methods Handbook* (EPA 1989f) describe some of the models available and provide guidance in selecting appropriate modeling techniques. Also, the Center for Exposure Assessment Modeling (CEAM -- Environmental Research Laboratory (ERL) Athens), the Source Receptor Analysis Branch (Office of Air Quality Planning and Standards, or OAQPS), and modelers in EPA regional offices can provide assistance in selecting appropriate models. Finally, Volume IV of the NTGS (EPA 1989c) provides guidance for air and atmospheric dispersion modeling for Superfund sites. Be sure to discuss the fate and transport models to be used in the exposure assessment with the RPM.

The level of effort to be expended in estimating exposure concentrations will depend on the type and quantity of data available, the level of detail required in the assessment, and the resources available for the assessment. In general, estimating exposure concentrations will involve analysis of site monitoring data and application of simple, screening-level analytical models. The most important factor in determining the level of effort will be the quantity and quality of the available data. In general, larger data sets will support the use of more sophisticated models.

Other considerations . When evaluating chemical contamination at a site, it is important to review the spatial distribution of the data and evaluate it in ways that have the most relevance to the pathway being assessed. In short, consider where the contamination is with respect to known or anticipated population activity patterns. Maps of both concentration distribution and activity patterns will be useful for the exposure assessment. It is the intersection of activity patterns and contamination that defines an exposure area. Data from random sampling or from systematic grid pattern sampling may be more representative of a given exposure pathway than data collected only from hot spots.

Generally, verified GC/MS laboratory data with adequate quality control will be required to support quantitative exposure assessment. Field screening data generally cannot be incorporated when estimating exposure concentrations because they are derived using less sensitive analytical methods and are subject to less stringent quality control.

Other areas to be considered in estimating exposure concentrations are as follows.

- Steady-state vs. non-steady-state conditions. Frequently, it may be necessary to assume steady-state conditions because the information required to estimate non-steady-state conditions (such as source depletion rate) is not readily available. This is likely to overestimate long-term exposure concentrations for certain pathways.

- Number and type of exposure parameters that must be assumed. In developing exposure models, values for site-specific parameters such as hydraulic conductivity, organic carbon content of soil, wind speed and direction, and soil type may be required. These values may be generated as part of the RI. In cases where these values are not available, literature values may be substituted. In the absence of applicable literature values, the assessor must consider if a reliable exposure concentration estimate can be made.

- Number and type of fate processes to be considered. In some cases, exposure modeling may be limited to considerations of mass balance, dilution, dispersion, and equilibrium partitioning. In other cases, models of more complex fate processes, such as chemical reaction, biodegradation, and photolysis may be needed. However, prediction of such fate processes requires significantly larger quantities of model calibration and validation data than required for less complex fate processes. For those sites where these more complex fate processes need to be modeled, be sure to consult with the RPM regarding the added data requirements.

6.5.2 ESTIMATE EXPOSURE CONCENTRATIONS IN GROUND WATER

Exposure concentrations in ground water can be based on monitoring data alone or on a combination of monitoring and modeling. In some cases, the exposure assessor may favor the use of monitoring data over the use of complex models to develop exposure concentrations. It is most appropriate to use ground-water sampling data as estimates of exposure concentrations when the sampling points correspond to exposure points, such as samples taken from a drinking water tap. However, samples taken directly from a domestic well or drinking water tap should be interpreted cautiously. For example, where the water is acidic, inorganic chemicals such as lead or copper may leach from the distribution system. Organic chemicals such as phthalates may migrate into water from plastic piping. Therefore, interpretations of these data should consider the type and operation of the pumping, storage, and distribution system involved.

Most of the time, data from monitoring wells will be used to estimate chemical concentrations at the exposure point. Several issues should be considered when using monitoring well data to estimate these concentrations. First, determine if the aquifer has sufficient production capacity and is of sufficient quality to support drinking water or other uses. If so, it generally should be assumed that water could be drawn from anywhere in the aquifer, regardless of the location of existing wells relative to the

contaminant plume. In a few situations, however, it may not be reasonable to assume that water will be drawn from directly beneath a specific source (e.g., a waste management unit such as a landfill) in the future. In these cases, it should be assumed that water could be drawn from directly adjacent to the source. Selection of the location(s) used to evaluate future ground-water exposures should be made in consultation with the RPM. Second, compare the construction of wells (e.g., drinking water wells) in the area with the construction of the monitoring wells. For example, drinking water wells may draw water from more than one aquifer, whereas individual monitoring wells are usually screened in a specific aquifer. In some cases it may be appropriate to separate data from two aquifers that have very limited hydraulic connection if drinking water wells in the area draw water from only one of them. Consult a hydrogeologist for assistance in the above considerations.

Another issue to consider is filtration of water samples. While filtration of ground-water samples provides useful information for understanding chemical transport within an aquifer (see Section 4.5.3 for more details), the use of filtered samples for estimating exposure is very controversial because these data may underestimate chemical concentrations in water from an unfiltered tap. Therefore, data from unfiltered samples should be used to estimate exposure concentrations. Consult with the RPM before using data from filtered samples.

Ground-water monitoring data are often of limited use for evaluating long-term exposure concentrations because they are generally representative of current site conditions and not long-term trends. Therefore, ground-water models may be needed to estimate exposure concentrations. Monitoring data should be used when possible to calibrate the models.

Estimating exposure concentrations in ground water using models can be a complex task because of the many physical and chemical processes that may affect transport and transformation in ground water. Among the important mechanisms that should be considered when estimating exposure concentrations in ground water are leaching from the surface, advection (including infiltration, flow through the unsaturated zone, and flow with ground water), dispersion, sorption (including adsorption, desorption, and ion exchange), and transformation (including biological degradation, hydrolysis, oxidation, reduction, complexation, dissolution, and precipitation). Another consideration is that not all chemicals may be dissolved in water, but may be present instead in nonaqueous phases that float on top of ground water or sink to the bottom of the aquifer.

The proper selection and application of soil and ground-water models requires a thorough understanding of the physical, chemical, and hydrogeologic characteristics of the site. SEAM (EPA 1988b) provides a discussion of the factors controlling soil and ground-water contaminant migration as well as descriptions of various soil and ground-water models. For more in-depth guidance on the selection and application of appropriate ground-water models, consult *Selection Criteria for Mathematical Models Used in Exposure Assessments: Ground-water Models* (EPA 1988c). As with all modeling, the assessor should carefully evaluate the applicability of the model to the site being evaluated, and should consult with a hydrogeologist as necessary.

If ground-water modeling is not used, current concentrations can be used to represent future concentrations in ground water assuming steady-state conditions. This assumption should be noted in the exposure assessment chapter and in the uncertainties and conclusions of the risk assessment.

6.5.3 ESTIMATE EXPOSURE CONCENTRATIONS IN SOIL

Estimates of current exposure concentrations in soil can be based directly on summarized monitoring data if it is assumed that concentrations remain constant over time. Such an assumption may not be appropriate for some chemicals and some sites where leaching, volatilization, photolysis, biodegradation, wind erosion, and surface runoff will reduce chemical concentrations over time. Soil monitoring data and site conditions should be carefully screened to identify situations where source depletion is likely to be important. SEAM (EPA 1988b) gives steady-state equations for estimating many of these processes. However, incorporating these processes into the calculation of exposure concentrations for soil involves considerable effort. If a modeling approach is not adopted in these situations, assume a constant concentration over time and base exposure concentrations on monitoring data. This assumption should be clearly documented.

In evaluating monitoring data for the assessment of soil contact exposures, the spatial distribution of the data is a critical factor. The spatial distribution of soil contamination can be used as a basis for estimating the average concentrations contacted over time if it is assumed that contact with soil is spatially random (i.e., if

contact with soil in all areas of the site is equally probable). Data from random sampling programs or samples from evenly spaced grid networks generally can be considered as representative of concentrations across the site. At many sites however, sampling programs are designed to characterize only obviously contaminated soils or hot spot areas. Care must be taken in evaluating such data sets for estimating exposure concentrations. Samples from areas where direct contact is not realistic (such as where a steep slope or thick vegetation prevents current access) should not be considered when estimating current exposure concentrations for direct contact pathways. Similarly, the depth of the sample should be considered; surface soil samples should be evaluated separately from subsurface samples if direct contact with surface soil or inhalation of wind blown dust are potential exposure pathways at the site.

In some cases, contamination may be unevenly distributed across a site, resulting in hot spots (areas of high contamination relative to other areas of the site). If a hot spot is located near an area which, because of site or population characteristics, is visited or used more frequently, exposure to the hot spot should be assessed separately. The area over which the activity is expected to occur should be considered when averaging the monitoring data for a hot spot. For example, averaging soil data over an area the size of a residential backyard (e.g., an eighth of an acre) may be most appropriate for evaluating residential soil pathways.

6.5.4 ESTIMATE EXPOSURE CONCENTRATIONS IN AIR

There are three general approaches to estimating exposure concentrations in air: (1) ambient air monitoring, (2) emission measurements coupled with dispersion modeling, and (3) emission modeling coupled with dispersion modeling. Whichever approach is used, the resulting exposure concentrations should be as representative as possible of the specific exposure pathways being evaluated. If long-term exposures are being evaluated, the exposure concentrations should be representative of long-term averages. If short-term exposures are of interest, measured or modeled peak concentrations may be most representative.

If monitoring data have been collected at a site, their adequacy for use in a risk assessment should be evaluated by considering how appropriate they are for the exposures being addressed. Volume II of the NTGS (EPA 1989b) provides guidance for measuring emissions and should be consulted when evaluating the appropriateness of emission data. See Chapter 4 (Section 4.5.5) for factors to consider when evaluating the appropriateness of ambient air monitoring data. As long as there are no significant analytical problems affecting air sampling data, background levels are not significantly higher than potential site-related levels, and site-related levels are not below the instrument detection limit, air monitoring data can be used to derive exposure concentrations. There still will be uncertainties inherent in using these data because they usually are not representative of actual long-term average air concentrations. This may be because there were only a few sample collection periods, samples were collected during only one type of meteorological or climatic condition, or because the source of the chemicals will change over time. These uncertainties should be mentioned in the risk assessment.

In the absence of monitoring data, exposure concentrations often can be estimated using models. Two kinds of models are used to estimate air concentrations: emission models that predict the rate at which chemicals may be released into the air from a source, and dispersion models that predict associated concentrations in air at potential receptor points.

Outdoor air modeling. Emissions may occur as a result of the volatilization of chemicals from contaminated media or as a result of the suspension of onsite soils. Models that predict emission rates for volatile chemicals or dust require numerous input parameters, many of which are site-specific. For volatile chemicals, emission models for surface water and soil are available in SEAM (EPA 1988b). Volume IV of the NTGS (EPA 1989c) also provides guidance for evaluating volatile emissions at Superfund sites. Emissions due to suspension of soils may result from wind erosion of exposed soil particles and from vehicular disturbances of the soil. To predict soil or dust emissions, EPA's fugitive dust models provided in AP42 (EPA 1985b) or models described in SEAM (1988b) may be used. Volume IV of the NTGS (EPA 1989c) also will be useful in evaluating fugitive dust emissions at Superfund sites. Be sure to critically review all models before use to determine their applicability to the situation and site being evaluated. If necessary, consult with air modelers in EPA regional offices, the Exposure

Assessment Group in EPA headquarters or the Source Receptor Analysis Branch in OAQPS.

After emissions have been estimated or measured, air dispersion models can be applied to estimate air concentrations at receptor points. In choosing a dispersion model, factors that must be considered include the type of source and the location of the receptor relative to the source. For area or point sources, EPA's Industrial Source Complex model (EPA 1987a) or the simple Gaussian dispersion models discussed in SEAM (EPA 1988b) can provide air concentrations around the source. Other models can be found in Volume IV of the NTGS (EPA 1989c). The Source Receptor Analysis Branch of OAQPS also can be contacted for assistance. Again, critically review all models for their applicability.

Indoor air modeling. Indoor emissions may occur as a result of transport of outdoor-generated dust or vapors indoors, or as a result of volatilization of chemicals indoors during use of contaminated water (e.g., during showering, cooking, washing). Few models are available for estimating indoor air concentrations from outside sources. For dust transport indoors, it can generally be assumed that indoor concentrations are less than those outdoors. For vapor transport indoors, concentrations indoors and outdoors can be assumed to be equivalent in most cases. However, at sites where subsurface soil gas or ground-water seepage are entering indoors, vapor concentrations inside could exceed those outdoors. Vapor concentrations resulting from indoor use of water may be greater than those outdoors, depending on the emission source characteristics, dispersion indoors, and indoor-outdoor air exchange rates. Use models discussed in the *Exposure Assessment Methods Handbook* (EPA 1989f) to evaluate volatilization of chemicals from indoor use of water.

6.5.5 ESTIMATE EXPOSURE CONCENTRATIONS IN SURFACE WATER

Data from surface water sampling and analysis may be used alone or in conjunction with fate and transport models to estimate exposure concentrations. Where the sampling points correspond to exposure points, such as at locations where fishing or recreational activities take place, or at the intake to a drinking water supply, the monitoring data can be used alone to estimate exposure concentrations. However, the data must be carefully screened. The complexity of surface water processes may lead to certain limitations in monitoring data. Among these are the following.

- **Temporal representativeness .** Surface water bodies are subject to seasonal changes in flow, temperature, and depth that may significantly affect the fate and transport of contaminants. Releases to surface water bodies often depend on storm conditions to produce surface runoff and soil erosion. Lakes are subject to seasonal stratification and changes in biological activity. Unless the surface water monitoring program has been designed to account for these phenomena, the data may not represent long-term average concentrations or short-term concentrations that may occur after storm events.

- **Spatial representativeness .** Considerable variation in concentration can occur with respect to depth and lateral location in surface water bodies. Sample locations should be examined relative to surface water mixing zones. Concentrations within the mixing zone may be significantly higher than at downstream points where complete mixing has taken place.

- **Quantitation limit limitations.** Where large surface water bodies are involved, contaminants that enter as a result of ground-water discharge or runoff from relatively small areas may be significantly diluted. Although standard analytical methods may not be able to detect chemicals at these levels, the toxic effects of the chemicals and/or their potential to bioaccumulate may nevertheless require that such concentrations be assessed.

- **Contributions from other sources.** Surface water bodies are normally subject to contamination from many sources (e.g., pesticide runoff, stormwater, wastewater discharges, acid mine drainage). Many of the chemicals associated with these sources may be difficult to distinguish from site-related chemicals. In many cases background samples will be useful in assessing site-related contaminants from other contaminants (see Section 4.4). However, there may be other cases where a release and transport model may be required to make the distinction.

Many analytical and numerical models are available to estimate the release of contaminants to surface water

and to predict the fate of contaminants once released. The models range from simple mass balance relationships to numerical codes that contain terms for chemical and biological reactions and interactions with sediments. In general, the level of information collected during the RI will tend to limit the use of the more complex models.

There are several documents that can be consulted when selecting models to estimate surface water exposure concentrations, including SEAM (EPA 1988b), the *Exposure Assessment Methods Handbook* (EPA 1989f), and *Selection Criteria for Mathematical Models Used in Exposure Assessments: Surface Water Models* (EPA 1987b). SEAM lists equations for surface water runoff and soil erosion and presents the basic mass balance relationships for estimating the effects of dilution. A list of available numerical codes for more complex modeling also is provided. The selection criteria document (EPA 1987b) provides a more in-depth discussion of numerical codes and other models. In addition, it provides guidelines and procedures for evaluating the appropriate level of complexity required for various applications. The document lists criteria to consider when selecting a surface water model, including: (1) type of water body, (2) presence of steady-state or transient conditions, (3) point versus non-point sources of contamination, (4) whether 1, 2, or 3 spatial dimensions should be considered, (5) the degree of mixing, (6) sediment interactions, and (7) chemical processes. Each of the referenced documents should be consulted prior to any surface water modeling.

6.5.6 ESTIMATE EXPOSURE CONCENTRATIONS IN SEDIMENTS

In general, use sediment monitoring data to estimate exposure concentrations. Sediment monitoring data can be expected to provide better temporal representativeness than surface water concentrations. This will especially be true in the case of contaminants such as PCBs, PAHs, and some inorganic chemicals, which are likely to remain bound to the sediments. When using monitoring data to represent exposure concentrations for direct contact exposures, data from surficial, near-shore sediments should be used.

If modeling is needed to estimate sediment exposure concentrations, consult SEAM (EPA 1988b). SEAM treats surface water and sediment together for the purpose of listing available models for the release and transport of contaminants. Models for soil erosion releases are equally applicable for estimating exposure concentrations for surface water and sediment. Many of the numerical models listed in SEAM and the surface water selection criteria document (EPA 1987b) contain sections devoted to sediment fate and transport.

6.5.7 ESTIMATE CHEMICAL CONCENTRATIONS IN FOOD

Fish and shellfish. Chemical concentrations in fish and shellfish may be measured or estimated. Site-specific measured values are preferable to estimated values, but before using such values, evaluate the sampling plan to determine if it was adequate to characterize the population and species of concern (see Section 4.5.6 for some sampling considerations). Also examine analytical procedures to determine if the quantitation limits were low enough to detect the lowest concentration potentially harmful to humans. Inadequate sampling or high levels of quantitation may lead to erroneous conclusions.

In the absence of adequate tissue measurements, first consider whether the chemical bioconcentrates (i.e., is taken up from water) or bioaccumulates (i.e., is taken up from food, sediment, and water). For example, low molecular weight volatile organic chemicals do not bioaccumulate in aquatic organisms to a great extent. Other chemicals accumulate in some species but not in others. For example, PAHs tend to accumulate in mollusk species but not in fish, which rapidly metabolize the chemicals. For those chemicals that bioconcentrate in aquatic species of concern, use the organism/water partition coefficient (i.e., bioconcentration factor, or BCF) approach to estimate steady-state concentrations. BCFs that estimate concentrations in edible tissue (muscle) are generally more appropriate for assessing human exposures from fish or shellfish ingestion than those that estimate concentrations in the whole body, although this is not true for all aquatic species or applicable to all human populations consuming fish or shellfish. When data from multiple experiments are available, select the BCF from a test that used a species most similar to the species of concern at the site, and multiply the BCF directly by the dissolved chemical concentration in water to obtain estimates of tissue concentrations. Be aware that the study from which the BCF is obtained should reflect a steady state or equilibrium condition, generally achieved over long-term exposures (although some chemicals may reach steady state rapidly in certain species). For some chemicals, BCFs may overestimate tissue levels in fish that may be exposed only for a short period of time.

When no BCF is available, estimate the BCF with a regression equation based on octanol/water partition coefficients (K_{ow}). Several equations are available in the literature. Those developed for chemicals with structural similarities to the chemical of concern should be used in preference to general equations because of better statistical correlations.

The regression equation approach to estimating BCFs can overestimate or underestimate concentrations in fish tissue depending upon the chemical of concern and the studies used to develop the regression equations. For example, high molecular weight PAHs (such as benz(a)pyrene) with high K_{ow} values lead to the prediction of high fish tissue residues. However, PAHs are rapidly metabolized in the liver, and do not appear to accumulate significantly in fish. Regression equations using K_{ow} cannot take into account such pharmacokinetics, and thus may overestimate bioconcentration. On the other hand, studies used to develop regression equations which were not representative of steady-state conditions will tend to underestimate BCFs.

Typical methods for estimating fish tissue concentrations are based on dissolved chemical concentrations in water. While chemicals present in sediment and biota may also bioaccumulate in fish, there are only limited data available to estimate contributions to fish from these sources. However, chemicals that readily adsorb to sediments, such as PCBs, can be present in surface water at concentrations below detection limits and still significantly bioaccumulate. Some models are available to assess the contribution of chemical concentrations in sediment to chemical concentrations in aquatic biota. CEAM (ERL Athens) may be of assistance in choosing and applying an appropriate model.

Plants. Site-related chemicals may be present in plants as a result of direct deposition onto plant surfaces, uptake from the soil, and uptake from the air. When possible, samples of plants or plant products should be used to estimate exposure concentrations. In the absence of monitoring data, several modeling approaches are available for estimating exposure concentrations in plants. Use of these models, however, can introduce substantial uncertainty into an exposure assessment.

If deposition onto plants is the source of the chemical, air deposition modeling can be used in conjunction with plant interception fractions to estimate uptake. The plant interception fraction can be estimated by methods published in the literature or can be developed for a specific crop by considering crop yield and the area of the plant available for deposition.

If soil contamination is the source of the chemical, calculate the concentration in plants by multiplying soil to plant partition coefficients by soil concentrations. Use the open literature or computerized data bases to obtain these coefficients from field, microcosm, or laboratory experiments that are applicable to the type of vegetation or crop of concern (see EPA 1985c sludge documents for some). In the absence of more specific information, use general BCFs published in the literature that are not crop-specific (see Baes *et al*. 1984 for some). When using these parameters, it is important to consider that many site-specific factors affect the extent of uptake. These factors include pH, the amount of organic material present in soil, and the presence of other chemicals.

When literature values are not available, consider equations published in the literature for estimating uptake into the whole plant, into the root, and translocation from the root into above ground parts (see Calamari *et al*. 1987). Such methods require physical/chemical parameters such as K_{ow} or molecular weight and were developed using a limited data base. Scientific judgment must always be applied in the development and application of any partition coefficient, and caution must be applied in using these values in risk assessment.

Terrestrial animals. Use tissue monitoring data when available and appropriate for estimating human exposure to chemicals in the terrestrial food chain. In the absence of tissue monitoring data, use transfer coefficients together with the total chemical mass ingested by an animal per day to estimate contaminant concentrations in meat, eggs, or milk. Data to support modeling of uptake by terrestrial animals generally are not available for birds, but are available for some mammalian species. Terrestrial mammals such as cattle are simultaneously exposed to chemicals from several sources such as water, soil, corn silage, pasture grass, and hay. Cattle ingest varying amounts of these sources per day, each of which will contain a different contaminant concentration. Because all sources can be important with regard to total body burden, an approach based upon the daily mass of chemical ingested per day is recommended because it can be applied to input from many sources.

Obtain transfer coefficients from the literature (see Ng *et al*. 1977, 1979, 1982; Baes *et al*. 1984 for some), or calculate them directly from feeding studies (see Jensen *et al*. 1981; Jensen and Hummel 1982; Fries *et al*. 1973; Van Bruwaene *et al*. 1984). In the absence of this information, use regression equations in the literature for the estimation of transfer coefficients (see Travis and Arms 1988). It is important to be aware that regression equations that use feeding study results from short-term exposures may underestimate meat or milk concentrations. In addition, regression equations which rely on K_{ow} values may overestimate exposures for chemicals such as benz(a)pyrene that are rapidly metabolized. Information on the amount of feed, soil and water ingested by dairy and beef cows is available in the literature and should be combined with chemical concentrations in these media to estimate a daily dose to the animal.

6.5.8 SUMMARIZE EXPOSURE CONCENTRATIONS FOR EACH PATHWAY

Summarize the exposure concentrations derived for each pathway. Exhibit 6-10 presents a sample format.

6.6 QUANTIFICATION OF EXPOSURE: ESTIMATION OF CHEMICAL INTAKE

This section describes the methodology for calculating chemical-specific intakes for the populations and exposure pathways selected for quantitative evaluation. The general equation for estimating intake was shown in Exhibit 6-9. Remember that the intakes calculated in this step are expressed as the amount of chemical at the exchange boundary (e.g., skin, lungs, gut) and available for absorption. Intake, therefore, is not equivalent to absorbed dose, which is the amount of a chemical absorbed into the blood stream.

EXHIBIT 6-10

EXAMPLE OF TABLE FORMAT FOR SUMMARIZING EXPOSURE CONCENTRATIONS

Populations/Pathways	Exposure Concentration	Comments
Current Residents		
Ingestion of ground water:		
Benzene	9 ug/L	Concentrations are the 95 percent upper confidence limit on the arithmetic average of measured concentrations in downgradient monitoring wells.
Chlordane	5.3 ug/L	
Cyanide	11 ug/L	
Direct contact with soil:		
Manganese	1200 mg/kg	Concentrations are the 95 percent upper confidence limit on the arithmetic average of measured concentrations in onsite surface soils.
Selenium	48 mg/kg	
Mercury	2 mg/kg	
Inhalation of dust:		
Manganese	1 mg/m^3	Concentrations are based on estimates of fugitive dust generation and dispersion to nearby homes. Concentration inputs for air model are 95 percent upper confidence limit on the arithmetic average of measured concentrations in onsite soil.
Selenium	0.04 mg/m^3	
Mercury	0.002 mg/m^3	

The sections that follow give standard equations for estimating human intakes for all possible exposure routes at a site. Values for equation variables are presented for use in evaluating residential exposures. Considerations for deriving pathway-specific variable values for populations other than residential (i.e., commercial/industrial or recreational) also are given. In general, both upper-bound (e.g., 95th percentile or maximum values) and average (mean or median) values are presented. These values can be used to calculate the RME or to evaluate uncertainty. A general discussion of which variable values should be used to calculate the RME was provided in Section 6.4.1; more specific guidance follows. A discussion of the uncertainty analysis is presented in Section 6.8.

The information presented below is organized by exposure medium and exposure route.

6.6.1 CALCULATE GROUND-WATER AND SURFACE WATER INTAKES

Individuals may be exposed to chemicals of potential concern in ground water and surface water by the following routes:

(1) ingestion of ground water or surface water used as drinking water;

(2) incidental ingestion of surface water while swimming; and

(3) dermal contact with ground water or surface water.

Inhalation exposures to chemicals that have volatilized from surface or ground water are covered in Section 6.6.3.

Intake from drinking water. Calculate residential intakes from ingestion of ground water or surface water used as drinking water, using the equation and variable values presented in Exhibit 6-11. As discussed in section 6.5.3, chemical concentration in water (CW) should be based on data from unfiltered samples. Develop pathway-specific variable values as necessary. Ingestion rates (IR) could be lower for residents who spend a portion of their day outside the home (e.g., at work). Also, exposure frequency (EF) may vary with land use. Recreational users and workers generally would be exposed less frequently than residents.

Intake from ingestion of surface water while swimming. Calculate intakes from incidental ingestion of surface water while swimming. Use the equation and variable values presented in Exhibit 6-12. Chemical concentration in water (CW) should represent unfiltered concentrations. Incidental ingestion rates (IR) while swimming have not been found in the available literature. SEAM (EPA 1988b) recommends using an incidental ingestion rate of 50 ml/hour of swimming. Exposure duration (ED) will generally be less for recreational users of a surface water compared to residents living near the surface water. Workers are not expected to be exposed via this pathway.

Intake from dermal contact. Calculate intakes from dermal contact with water while swimming, wading, etc., or during household use (e.g., bathing).

Use the equation and variable values presented in Exhibit 6-13. In this case, the calculated exposure is actually the absorbed dose, not the amount of chemical that comes in contact with the skin (i.e., intake). This is because permeability constants (PC) reflect the movement of the chemical across the skin to the stratum corneum and into the bloodstream. Be sure to record this information in the summary of exposure assessment results so that the calculated intake is compared to an appropriate toxicity reference value in the risk characterization chapter. Note that PC are based on an equilibrium partitioning and likely result in an over-estimation of absorbed dose over short exposure periods (e.g., < 1 hr). The open literature should be consulted for chemical-specific PC values. The values in SEAM (EPA 1988b) are currently being reviewed and should not be used at this time. If chemical-specific PC values are not available, the permeability of water can be used to derive a default value. (See Blank *et al.* [1984] for some values [e.g., 8.4×10^{-4} cm/hr].) Note that this approach may underestimate dermal permeability for some organic chemicals.

EXHIBIT 6-11

RESIDENTIAL EXPOSURE: INGESTION OF CHEMICALS IN DRINKING WATER [a] (AND BEVERAGES MADE USING DRINKING WATER)

Equation:

$$\text{Intake (mg/kg-day)} = \frac{CW \times IR \times EF \times ED}{BW \times AT}$$

Where:

CW = Chemical Concentration in Water (mg/liter)
IR = Ingestion Rate (liters/day)
EF = Exposure Frequency (days/year)
ED = Exposure Duration (years)
BW = Body Weight (kg)
AT = Averaging time (period over which exposure is averaged -- days)

Variable Values:

CW: Site-specific measured or modeled value

IR: 2 liters/day (adult, 90th percentile; EPA 1989d)
1.4 liters/day (adult, average; EPA 1989d)
Age-specific values (EPA 1989d)

EF: Pathway-specific value (for residents, usually daily -- 365 days/year)

ED: 70 years (lifetime; by convention)
30 years (national upper-bound time (90th percentile) at one residence; EPA 1989d)
9 years (national median time (50th percentile) at one residence; EPA 1989d)

BW: 70 kg (adult, average; EPA 1989d)
Age-specific values (EPA 1985a, 1989d)

AT: Pathway-specific period of exposure for noncarcinogenic effects (i.e., ED x 365 days/year), and 70 year lifetime for carcinogenic effects (i.e., 70 years x 365 days/year).

[a] *See Section 6.4.1 and 6.6.1 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, combine 95th or 90th percentile values for contact rate and exposure frequency and duration variables.*

EXHIBIT 6-12

RESIDENTIAL EXPOSURE: INGESTION OF CHEMICALS IN SURFACE WATER WHILE SWIMMING[a]

Equation:

$$\text{Intake (mg/kg-day)} = \frac{\text{CW x IR x EF x ED}}{\text{BW x AT}}$$

Where:

CW = Chemical Concentration in Water (mg/liter)
CR = Contact Rate (liters/hour)
IR = Ingestion Rate (liters/day)
ET = Exposure Time (hours/event)
EF = Exposure Frequency (events/year)
ED = Exposure Duration (years)
BW = Body Weight (kg)
AT = Averaging time (period over which exposure is averaged -- days)

Variable Values:

CW: Site-specific measured or modeled value

CR: 50 ml/hour (EPA 1989d)

EF: Pathway-specific value

EF: Pathway-specific value (should consider local climatic conditions [e.g., number of days above a given temperature] and age of potentially exposed population)
7 days/year (national average for swimming; USDOI in EPA 1988b, EPA 1989d)

ED: 70 years (lifetime; by convention)
30 years (national upper-bound time (90th percentile) at one residence; EPA 1989d)
9 years (national median time (50th percentile) at one residence; EPA 1989d)

BW: 70 kg (adult, average; EPA 1989d)
Age-specific values (EPA 1985a, 1989d)

AT: Pathway-specific period of exposure for noncarcinogenic effects (i.e., ED x 365 days/year), and 70 year lifetime for carcinogenic effects (i.e., 70 years x 365 days/year).

[a] *See Section 6.4.1 and 6.6.1 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, combine 95th or 90th percentile values for contact rate and exposure frequency and duration variables.*

EXHIBIT 6-13

RESIDENTIAL EXPOSURE: DERMAL CONTACT WITH CHEMICALS IN WATER[a]

Equation:

$$\text{Absorbed dose (mg/kg-day)} = \frac{CW \times SA \times PC \times ET \times EF \times ED \times CF}{BW \times AT}$$

Where:

CW = Chemical Concentration in Water (mg/liter)
SA = Skin Surface Area Available for Contact (cm^2)
PC = Chemical-specific Dermal Permeability Constant (cm/hr)
ET = Exposure Time (hours/day)
EF = Exposure Frequency (days/year)
ED = Exposure Duration (years)
CF = Volumetric Conversion Factor for Water (1 liter/1000 cm^3)
BW = Body Weight (kg)
AT = Averaging time (period over which exposure is averaged -- days)

Variable Values:

CW: Site-specific measured or modeled value

SA:

50th Percentile Total Body Surface Area (m^2) (EPA 1989d, 1985a)

AGE (YRS)	MALE	FEMALE
3 < 6	0.728	0.711
6 < 9	0.931	0.919
9 < 12	1.16	1.16
12 < 15	1.49	1.48
15 < 18	1.75	1.60
Adult	1.94	1.69

50th Percentile Body Part-specific Surface Areas for Males (m^2) (EPA 1989d, 1985a)

AGE (YRS)	ARMS	HANDS	LEGS	
3 < 4	0.096	0.040	0.18	
6 < 7	0.11	0.041	0.24	
9 < 10	0.13	0.057	0.31	
Adult		0.23	0.082	0.55

[a] See Section 6.4.1 and 6.6.1 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, combine 95th or 90th percentile values for contact rate and exposure frequency and duration variables. Use 50th percentile values for SA; see text for rationale.

(continued)

EXHIBIT 6-13 (continued)

RESIDENTIAL EXPOSURE: DERMAL CONTACT WITH CHEMICALS IN WATER[a]

NOTE: ***Values for children were calculated using age-specific body areas and the average percentage of total body surface area represented by particular body parts in children, presented in EPA 1985a. Values for adults presented in EPA 1989d or calculated from information presented in EPA 1985a. Information on surface area of other body parts (e.g. head, feet) and for female children and adults also is presented in EPA 1985a, 1989d. Differences in body part surface areas between sexes is negligible.***

PC: **Consult open literature for values [Note that use of PC values results in an estimate of absorbed dose.]**

ET: **Pathway-specific value (consider local activity patterns if information is available)**
2.6 hrs/day (national average for swimming; USDOI in EPA 1988b, EPA 1989d)

EF: **Pathway-specific value (should consider local climatic conditions [e.g., number of days above a given temperature] and age of potentially exposed population)**
7 days/year (national average for swimming; USDOI in EPA 1988b, EPA 1989d)

ED: **70 years (lifetime; by convention)**
30 years (national upper-bound time (90th percentile) at one residence; EPA 1989d)
9 years (national median time (50th percentile) at one residence; EPA 1989d)

CF: **1 liter/1000 cm^3**

BW: **70 kg (adult, average; EPA 1989d)**
Age-specific values (EPA 1985a, 1989d)

AT: **Pathway-specific period of exposure for noncarcinogenic effects (i.e., ED x 365 days/year), and 70 year lifetime for carcinogenic effects (i.e., 70 years x 365 days/year).**

[a] ***See Section 6.4.1 and 6.6.1 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, combine 95th or 90th percentile values for contact rate and exposure frequency and duration variables.***

To calculate the reasonable maximum exposure for this pathway, 50th percentile values, instead of 95th percentile values, are used for the area of exposed skin (SA). This is because surface area and body weight are strongly correlated and 50th percentile values are most representative of the surface area of individuals of average weight (e.g., 70 kg) which is assumed for this and all other exposure pathways. Estimates of exposure for this pathway are still regarded as conservative because generally conservative assumptions are used to estimate dermal absorption (PC) and exposure frequency and duration.

Consider pathway-specific variations for the intake variables. SA will vary with activity and the extent of clothing worn. For example, a greater skin surface area would be in contact with water during bathing or swimming than when wading. Worker exposure via this pathway will depend on the type of work performed at the site, protective clothing worn, and the extent of water use and contact.

6.6.2 CALCULATE SOIL, SEDIMENT, OR DUST INTAKES

Individuals may be exposed to chemicals of potential concern in soil, sediment, or dust by the following routes:

(1) incidental ingestion; and
(2) dermal contact.

Inhalation exposures to airborne soil or dust are discussed in Section 6.6.3.

Incidental ingestion. Calculate intakes from incidental ingestion of chemicals in soil by residents using the equation and variable values presented in Exhibit 6-14. Consider population characteristics that might influence variable values. Exposure duration (ED) may be less for workers and recreational users.

The value suggested for ingestion rate (IR) for children 6 years old and younger are based primarily on fecal tracer studies and account for ingestion of indoor dust as well as outdoor soil. These values should be viewed as representative of long-term average daily ingestion rates for children and should be used in conjunction with an exposure frequency of 365 days/year. A term can be used to account for the fraction of soil or dust contacted that is presumed to be contaminated (FI). In some cases, concentrations in indoor dust can be equal to those in outdoor soil. Conceivably, in these cases, FI could be equal to 1.0.

For ingestion of chemicals in sediment, use the same equation as that used for ingestion of soil. Unless more pathway-specific values can be found in the open literature, use as default variable values the same values as those used for ingestion of soil. In most instances, contact and ingestion of sediments is not a relevant pathway for industrial/commercial land use (a notable exception to this could be workers repairing docks).

Dermal contact. Calculate exposure from dermal contact with chemicals in soil by residents using the equation and variable values presented in Exhibit 6-15. As was the case with exposure to chemicals in water, calculation of exposure for this pathway results in an estimate of the absorbed dose, not the amount of chemical in contact with the skin (i.e., intake). Absorption factors (ABS) are used to reflect the desorption of the chemical from soil and the absorption of the chemical across the skin and into the blood stream. Consult the open literature for information on chemical-specific absorption factors. In the absence of chemical-specific information, use conservative assumptions to estimate ABS.

Again, as with dermal exposure to water, 50th percentile body surface area (SA) values are used to estimate contact rates. These values are used along with average body weight because of the strong correlation between surface area and body weight. Contact rates may vary with time of year and may be greater for individuals contacting soils in the warmer months of the year when less clothing is worn (and hence, more skin is available for contact). Adherence factors (AF) are available for few soil types and body parts. The literature should be reviewed to derive AF values for other soil types and other body parts. Exposure frequency (EF) is generally determined using site-specific information and professional judgment.

EXHIBIT 6-14

RESIDENTIAL EXPOSURE: INGESTION OF CHEMICALS IN SOIL[a]

Equation:

$$\text{Intake (mg/kg-day)} = \frac{CS \times IR \times CF \times FI \times EF \times ED}{BW \times AT}$$

Where:

CS = Chemical Concentration in Soil (mg/kg)
IR = Ingestion Rate (mg soil/day)
CF = Conversion Factor (10^{-6} kg/mg)
FI = Fraction Ingested from Contaminated Source (unitless)
EF = Exposure Frequency (days/year)
ED = Exposure Duration (years)
BW = Body Weight (kg)
AT = Averaging time (period over which exposure is averaged -- days)

Variable Values:

CS: Site-specific measured value

IR: 200 mg/day (children, 1 through 6 years old; EPA 1989g)
100 mg/day (age groups greater than 6 years old; EPA 1989g)

NOTE: IR values are default values and could change based on site-specific or other information. Research is currently ongoing to better define ingestion rates. IR values do not apply to individuals with abnormally high soil ingestion rates (i.e., pica).

CF: 10^{-6} kg/mg

FI: Pathway-specific value (should consider contaminant location and population activity patterns)

EF: 365 days/year

ED: 70 years (lifetime; by convention)
30 years (national upper-bound time (90th percentile) at one residence; EPA 1989d)
9 years (national median time (50th percentile) at one residence; EPA 1989d)

BW: 70 kg (adult, average; EPA 1989d)
16 kg (children 1 through 6 years old, 50th percentile; EPA 1985a)

AT: Pathway-specific period of exposure for noncarcinogenic effects (i.e., ED x 365 days/year), and 70 year lifetime for carcinogenic effects (i.e., 70 years x 365 days/year).

[a] *See Section 6.4.1 and 6.6.2 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, use 95th or 90th percentile values for contact rate and exposure frequency and duration variables.*

EXHIBIT 6-15

RESIDENTIAL EXPOSURE: DERMAL CONTACT WITH CHEMICALS IN SOIL[a]

Equation:

$$\text{Absorbed Dose (mg/kg-day)} = \frac{CS \times CF \times SA \times AF \times ABS \times EF \times ED}{BW \times AT}$$

Where:

CS = Chemical Concentration in Soil (mg/kg)
CF = Conversion Factor (10^{-6} kg/mg)
SA = Skin Surface Area Available for Contact (cm^2/event)
AF = Soil to Skin Adherence Factor (mg/cm^2)
ABS = Absorption Factor (unitless)
EF = Exposure Frequency (events/year)
ED = Exposure Duration (years)
BW = Body Weight (kg)
AT = Averaging Time (period over which exposure is averaged -- days)

Variable Values:

CS: Based on site-specific measured value

CF: (10^{-6} kg/mg)

SA:

50th Percentile Total Body Surface Area (m^2) (EPA 1989d, 1985a)

AGE (YRS)	MALE	FEMALE
3 < 6	0.728	0.711
6 < 9	0.931	0.919
9 < 12	1.16	1.16
12 < 15	1.49	1.48
15 < 18	1.75	1.60
Adult	1.94	1.69

50th Percentile Body Part-specific Surface Areas for Males (m^2) (EPA 1989d, 1985a)

AGE (YRS)	ARMS	HANDS	LEGS	
3 < 4	0.096	0.040	0.18	
6 < 7	0.11	0.041	0.24	
9 < 10	0.13	0.057	0.31	
Adult		0.23	0.082	0.55

NOTE: Values for children were calculated using age-specific body surface areas and the average percentage of total body surface area represented by particular body parts in children, presented in EPA 1985a. Values for adults presented in EPA 1989d or calculated from information presented in EPA 1985a.

[a] *See Section 6.4.1 and 6.6.1 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, combine 95th or 90th percentile values for contact rate and exposure frequency variables. Use 50th percentile values for SA; see text for rationale.*

(continued)

EXHIBIT 6-15 (continued)

RESIDENTIAL EXPOSURE: DERMAL CONTACT WITH CHEMICALS IN SOIL[a]

NOTE (continued): Information on surface area of other body parts (e.g., head, feet) and for female children and adults also is presented in EPA 1985a, 1989d. Differences in body part surface areas between sexes is negligible.

AF: 1.45 mg/cm^2 -- commercial potting soil (for hands; EPA 1989d, EPA 1988b)
2.77 mg/cm^2 -- kaolin clay (for hands; EPA 1989d, EPA 1988b)

ABS: Chemical-specific value (this value accounts for desorption of chemical from the soil matrix and absorption of chemical across the skin; generally, information to support a determination of ABS is limited -- see text)

EF: Pathway-specific value (should consider local weather conditions [e.g., number of rain, snow and frost-free days] and age of potentially exposed population)

ED: 70 years (lifetime; by convention)
30 years (national upper-bound time (90th percentile) at one residence; EPA 1989d)
9 years (national median time (50th percentile) at one residence; EPA 1989d)

BW: 70 kg (adult, average; EPA 1989d)
Age-specific values (EPA 1985a, 1989d)

AT: Pathway-specific period of exposure for noncarcinogenic effects (i.e., ED x 365 days/year), and 70 year lifetime for carcinogenic effects (i.e., 70 years x 365 days/year)

[a] *See Section 6.4.1 and 6.6.1 for a discussion of which variable values should be used to calculate the reason-able maximum exposure. In general, combine 95th or 90th percentile values for contact rate and exposure frequency and duration variables.*

"Best guess" values for children potentially useful in risk assessments are 3 times/week for fall and spring days (>32°F) and 5 times/week for summer days when children are not attending school. As discussed previously, in some cases, concentrations in indoor dust could be equal to that in outdoor environments. Therefore, at some sites, EF could be 365 days/year. Worker and recreational user contact rates are dependent on the type of activity at the site. Exposure duration (ED) and exposure frequency (EF) may be lower for workers and recreational users.

For dermal contact with sediment or dust, use the same equation as that for dermal contact with soil. As default values, also use the variable values given for dermal contact with soil unless more pathway-specific values can be found in the open literature. Adherence factors for some sediments (particularly sandy sediments) are likely to be much less than for soils because contact with water may wash the sediment off the skin. Exposure frequency for sediments also is probably lower than that for soils at many sites.

6.6.3 CALCULATE AIR INTAKES

Individuals may be exposed to chemicals of potential concern in air by inhalation of chemicals in the vapor phase or adsorbed to particulates. Dermal absorption of vapor phase chemicals is considered to be lower than inhalation intakes in many instances and generally is not considered in Superfund exposure assessments.

As with other pathways, the inhalation intakes are expressed in units of mg/kg-day. The combination of inhalation intakes with inhalation RfDs (expressed in concentration units of mg/m^3) will be discussed in Chapters 7 and 8.

Inhalation of vapor-phase chemicals . Calculate intakes from inhalation of vapor phase chemicals using the equation and variable values presented in Exhibit 6-16. Consider variations with land use. Exposure time (ET) will generally be less for workers and recreational users. For exposure times less than 24 hours per day, an hourly inhalation rate (IR) based on activity, age, and sex should be used instead of the daily IR values. Exposure duration (ED) may also be less for workers and recreational users.

Inhalation of particulate phase chemicals. Calculate intakes from inhalation of particulate phase chemicals by modifying the equations and variable values presented in Exhibit 6-16 for vapor-phase exposures. Derive inhalation estimates using the particulate concentration in air, the fraction of the particulate that is respirable (i.e., particles 10 um or less in size) and the concentration of the chemical in the respirable fraction. Note that it may be necessary to adjust intakes of particulate phase chemicals if they are to be combined with toxicity values that are based on exposure to the chemical in the vapor phase. This adjustment is done in the risk characterization step.

6.6.4 CALCULATE FOOD INTAKES

Individuals may be exposed by ingestion of chemicals of potential concern that have accumulated in food. The primary food items of concern are:

(1) fish and shellfish;

(2) vegetables and other produce; and

(3) meat, eggs, and dairy products (domestic and game species).

Ingestion of fish and shellfish. Calculate intakes from ingestion of fish and shellfish using the equation and variable values given in Exhibit 6-17. Exposure will depend in part on the availability of suitable fishing areas. The chemical concentration in fish or shellfish (CF) should be the concentration in the edible tissues (when available). The edible tissues will vary with aquatic species and with population eating habits. Residents near major commercial or recreational fisheries or shell fisheries are likely to ingest larger quantities of locally caught fish and shellfish than inland residents. In most instances, workers are not likely to be exposed via this pathway, although at some sites this may be possible.

Ingestion of vegetables or other produce. Calculate intakes from ingestion of contaminated vegetables or other produce using the equation and variable values given in Exhibit 6-18. This pathway will be most significant for farmers and for rural and urban residents consuming homegrown fruits and vegetables. For contaminated backyard gardens, the fraction of food ingested that is contaminated (FI) can be estimated using information on the fraction of fruits or vegetables consumed daily that is home grown (HF). EPA (1989d) provides HF values for fruit (0.20, average; 0.30 worst-case) and vegetables (0.25, average; 0.40,

EXHIBIT 6-16

RESIDENTIAL EXPOSURE: INHALATION OF AIRBORNE (VAPOR PHASE) CHEMICALS [a] [b]

Equation:

$$\text{Intake (mg/kg-day)} = \frac{\text{CA x IR x ET x EF x ED}}{\text{BW x AT}}$$

Where:

CA = Chemical Concentration in Air (mg/m^3)
IR = Inhalation Rate (m^3/hour)
ET = Exposure Time (hours/day)
EF = Exposure Frequency (days/year)
ED = Exposure Duration (years)
BW = Body Weight (kg)
AT = Averaging Time (period over which exposure is averaged – days)

Variable Values:

CA: Site-specific measured or modeled value

IR: 30 m^3/day (adult, suggested upper bound value; EPA 1989d)
20 m^3/day (adult, average; EPA 1989d)
Hourly rates (EPA 1989d)
Age-specific values (EPA 1985a)
Age, sex, and activity based values (EPA 1985a)
0.6 m^3/hr – showering (all age groups; EPA 1989d)

ET: Pathway-specific value (dependent on duration of exposure-related activities)
12 minutes – showering (90th percentile; EPA 1989d)
7 minutes – showering (50th percentile; EPA 1989d)

EF: Pathway-specific value (dependent on frequency of showering or other exposure-related activities)

ED: 70 years (lifetime; by convention)
30 years (national upper-bound time (90th percentile) at one residence; EPA 1989d)
9 years (national median time (50th percentile) at one residence; EPA 1989d)

BW: 70 kg (adult, average; EPA 1989d)
Age-specific values (EPA 1985a, 1989d)

AT: Pathway-specific period of exposure for noncarcinogenic effects (i.e., ED x 365 days/year), and 70 year lifetime for carcinogenic effects (i.e., 70 years x 365 days/year).

[a] *See Section 6.4.1 and 6.6.3 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, use 95th or 90th percentile values for contact rate and exposure frequency and duration variables.*

[b] *The equation and variable values for vapor phase exposure can be used with modification to calculate particulate exposure. See text.*

EXHIBIT 6-17

RESIDENTIAL EXPOSURE: FOOD PATHWAY -- INGESTION OF CONTAMINATED FISH AND SHELLFISH [a]

Equation:

$$\text{Intake (mg/kg-day)} = \frac{CF \times IR \times FI \times EF \times ED}{BW \times AT}$$

Where:

CF = Chemical Concentration in Fish (mg/kg)
IR = Ingestion Rate (kg/meal)
FI = Fraction Ingested from Contaminated Source (unitless)
EF = Exposure Frequency (meals/year)
ED = Exposure Duration (years)
BW = Body Weight (kg)
AT = Averaging time (period over which exposure is averaged – days)

Variable Values:

CF: Site-specific measured or modeled value

IR: 0.284 kg/meal (95th percentile for fin fish; Poa *et al.* 1982)
0.113 kg/meal (50th percentile for fin fish; Poa *et al.* 1982)

132 g/day (95th percentile daily intakes averaged over three days for consumers of fin fish; Poa *et al.* 1982)
38 g/day (50th percentile daily intake averaged over three days for consumers of fin fish; Poa *et al.* 1982)
6.5 g/day (daily intake averaged over a year; EPA 1989d. NOTE: Daily intake values should be used in conjunction with an exposure frequency of 365 days/year.)
Specific values for age, sex, race, region and fish species are available (EPA 1989d, 1989h)

FI: Pathway-specific value (should consider local usage patterns)

EF: Pathway-specific value (should consider local population patterns if information is available)
48 days/year (average per capita for fish and shellfish; EPA Tolerance Assessment System in EPA 1989h)

ED: 70 years (lifetime; by convention)
30 years (national upper-bound time (90th percentile) at one residence; EPA 1989d)
9 years (national median time (50th percentile) at one residence; EPA 1989d)

BW: 70 kg (adult, average; EPA 1989d)
Age-specific values (EPA 1985a, 1989d)

AT: Pathway-specific period of exposure for noncarcinogenic effects (i.e., ED x 365 days/year), and 70 year lifetime for carcinogenic effects (i.e., 70 years x 365 days/year).

[a] *See Section 6.4.1 and 6.6.4 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, use 95th or 90th percentile values for intake rate and exposure frequency and duration variables.*

EXHIBIT 6-18

RESIDENTIAL EXPOSURE: FOOD PATHWAY -- INGESTION OF CONTAMINATED FRUITS AND VEGETABLES [a]

Equation:

$$\text{Intake (mg/kg-day)} = \frac{CF \times IR \times FI \times EF \times ED}{BW \times AT}$$

Where:

CF = Contaminant Concentration in Food (mg/kg)
IR = Ingestion Rate (kg/meal)
FI = Fraction Ingested from Contaminated Source (unitless)
EF = Exposure Frequency (meals/year)
ED = Exposure Duration (years)
BW = Body Weight (kg)
AT = Averaging time (period over which exposure is averaged -- days)

Variable Values:

CF: Site-specific measured value or modeled value based on soil concentration and plant:soil accumulation factor or deposition factors

IR: Specific values for a wide variety of fruits and vegetables are available (Poa et al. 1982)

FI: Pathway-specific value (should consider location and size of contaminated area relative to that of residential areas, as well as anticipated usage patterns)

EF: Pathway-specific value (should consider anticipated usage patterns)

ED: 70 years (lifetime; by convention)
30 years (national upper-bound time (90th percentile) at one residence; EPA 1989d)
9 years (national median time (50th percentile) at one residence; EPA 1989d)

BW: 70 kg (adult, average; EPA 1989d)
Age-specific values (EPA 1985a, 1989d)

AT: Pathway-specific period of exposure for noncarcinogenic effects (i.e., ED x 365 days/year), and 70 year lifetime for carcinogenic effects (i.e., 70 years x 365 days/year).

[a] *See Section 6.4.1 and 6.6.4 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, use 95th or 90th percentile values for contact rate and exposure frequency and duration variables.*

worst-case). (Worst-case values can be used as estimates of the 95th percentile value.) Pao *et al*. (1982) provides specific values for a variety of fruits and vegetables.

Workers are not likely to be exposed via this pathway. Recreational users could be exposed from consuming wild fruits or vegetables from the site, although such exposures are likely to be negligible.

Ingestion of meat, eggs, and dairy products. Calculate intakes from ingestion of contaminated meat and dairy products using the equation and variable values given in Exhibit 6-19. Derive pathway-specific values as necessary. Rural residents may consume poultry as well as livestock and wild game that have been exposed to contaminants at the site. The fraction of food ingested daily that is contaminated (FI) can be estimated for beef and dairy products using information provided in EPA (1989d) on the fraction of these foods that is homegrown (HF). HF for beef is estimated to be 0.44 (average) and 0.75 (worst-case). HF for dairy products is estimated to be 0.40 (average) and 0.75 (worst-case). (Worst-case values can be used as estimates of the 95th percentile value.) Consider land-use variations. Workers are not likely to be exposed via this pathway. Exposure duration (ED) and exposure frequency (EF) will likely be less for recreational users (e.g., hunters).

6.7 COMBINING CHEMICAL INTAKES ACROSS PATHWAYS

As discussed previously, the RME at a site reflects the RME for a pathway as well as the RME across pathways. A given population may be exposed to a chemical from several exposure routes. For example, residents may be exposed to chemicals in ground water via ingestion of drinking water and via inhalation of chemicals that have volatilized from ground water during its use. They also could be exposed to chemicals in vapors or dust that have migrated from the site. To calculate an exposure that is a reasonable maximum across pathways, it may be necessary to combine the RME for one pathway with an estimate of more typical exposure for another pathway (see Section 8.3.1). The average variable values identified in the previous sections can be used to calculate intakes for these more typical exposures. At this point in the assessment, estimated intakes are not summed across pathways; this is addressed in the risk characterization chapter. However, the assessor should organize the results of the previous exposure analyses (including any estimates of typical exposure) by grouping all applicable exposure pathway for each exposed population. This organization will allow risks from appropriate exposures to be combined in the risk characterization chapter (see Exhibit 6-22 for a sample summary format).

6.8 EVALUATING UNCERTAINTY

The discussion of uncertainty is a very important component of the exposure assessment. Based on the sources and degree of uncertainty associated with estimates of exposure, the decision-maker will evaluate whether the exposure estimates are the maximum exposures that can be reasonably expected to occur. Section 8.4 provides a discussion of how the exposure uncertainty analysis is incorporated into the uncertainty analysis for the entire risk assessment.

The discussion of uncertainty in the exposure assessment chapter should be separated into two parts. The first part is a tabular summary of the values used to estimate exposure and the range of these values. The table should include the variables that appear in the exposure equation as well as those used to estimate exposure concentrations (e.g., model variables). A simple example of this table is shown in Exhibit 6-20. For each variable, the table should include the range of possible values, the midpoint of the range (useful values for this part are given in Exhibits 6-11 through 6-19), and the value used to estimate exposure. In addition, a brief description of the selection rationale should be included. The discussion that accompanies the table in the exposure assessment chapter should identify which variables have the greatest range and provide additional justification for the use of values that may be less certain.

EXHIBIT 6-19

RESIDENTIAL EXPOSURE: FOOD PATHWAY -- INGESTION OF CONTAMINATED MEAT, EGGS, AND DAIRY PRODUCTS [a]

Equation:

$$\text{Intake (mg/kg-day)} = \frac{CF \times IR \times FI \times EF \times ED}{BW \times AT}$$

Where:

CF = Chemical Concentration in Food (mg/kg)
IR = Ingestion Rate (kg/meal)
FI = Fraction Ingested from Contaminated Source (unitless)
EF = Exposure Frequency (meals/year)
ED = Exposure Duration (years)
BW = Body Weight (kg)
AT = Averaging time (period over which exposure is averaged -- days)

Variable Values:

CF: Site-specific measured or modeled value. Based on soil concentrations, plant (feed) accumulation factors, and feed-to-meat or feed-to-dairy product transfer coefficients

IR: 0.28 kg/meal -- beef (95th percentile; Poa *et al.* 1982)
0.112 kg/meal -- beef (50th percentile; Poa *et al.* 1982)
Specific values for other meats are available (Poa *et al.* 1982)

0.150 kg/meal -- eggs (95th percentile; Poa *et al.* 1982)
0.064 kg/meal -- eggs (50th percentile; Poa *et al.* 1982)

Specific values for milk, cheese and other dairy products are available (Poa et al. 1982)

FI: Pathway-specific value (should consider location and size of contaminated area relative to that of residential areas, as well as anticipated usage patterns)

EF: Pathway-specific value (should consider anticipated usage patterns)

ED: 70 years (lifetime; by convention)
30 years (national upper-bound time (90th percentile) at one residence; EPA 1989d)
9 years (national median time (50th percentile) at one residence; EPA 1989d)

BW: 70 kg (adult, average; EPA 1989d)
Age-specific values (EPA 1985a, 1989d)

AT: Pathway-specific period of exposure for noncarcinogenic effects (i.e., ED x 365 days/year), and 70 year lifetime for carcinogenic effects (i.e., 70 years x 365 days/year).

[a] *See Section 6.4.1 and 6.6.4 for a discussion of which variable values should be used to calculate the reasonable maximum exposure. In general, use 95th or 90th percentile values for contact rate and exposure frequency and duration.*

EXHIBIT 6-20

EXAMPLE OF TABLE FORMAT FOR SUMMARIZING VALUES USED TO ESTIMATE EXPOSURE

Variable	Range	Midpoint	Value Used	Brief Rationale
PCB concentration in soil (mg/kg)	ND - 3,500	250 (arithmetic mean)		
Chronic exposure (mg/kg)			1,400	95th percentile upperbound estimate of mean concentration
Acute exposure (mg/kg)			3,500	Maximum detected concentration
Adult soil ingestion rate (mg/d)	0 - 170	17 (arithmetic mean)	100	Range based on assumptions regarding soil adherence and percent ingestion. Value used is from EPA 1989g.
Exposure frequency (days/wk)	1 - 7	3	5	Best professional judgement.
Exposure duration (years)	1 - 20	10	20	Best professional judgement.

The second part of the uncertainty discussion is to summarize the major assumptions of the exposure assessment, to discuss the uncertainty associated with each, and to describe how this uncertainty is expected to affect the estimate of exposure. Sources of uncertainty that should be addressed include 1) the monitoring data, which may or may not be representative of actual conditions at the site; 2) the exposure models, assumptions and input variables used to estimate exposure concentrations; and 3) the values of the intake variables used to calculate intakes. Each of these sources should be discussed in the summary section of the exposure assessment. A table may be useful in summarizing this information. Exhibit 6-21 presents a sample format.

A supplemental approach to uncertainty analysis is to use analytical methods (e.g., first-order uncertainty analysis) or numerical methods (e.g., Monte Carlo analysis). These methods and their limitations are described in greater detail in Section 8.4 It is recommended that these analyses be used only after approval of the EPA project manager, and then, only as a part of the uncertainty analysis (and not as a basis for the reasonable maximum exposure).

6.9 SUMMARIZING AND PRESENTING THE EXPOSURE ASSESSMENT RESULTS

At this point, the exposure assessor should summarize the results of the exposure assessment. The summary information should be presented in table format and should list the estimated chemical-specific intakes for each pathway. The pathways should be grouped by population so that risks can be combined across pathways as appropriate. The summary information should be further grouped by current and future use categories. Within these categories, subchronic and chronic daily intakes should be summarized separately. Exhibit 6-22 presents a sample format for this summary information. In addition to the summary table, provide sample calculations for each pathway, to aid in the review of the calculations.

EXHIBIT 6-21

EXAMPLE OF AN UNCERTAINTY TABLE FOR EXPOSURE ASSESSMENT

ASSUMPTION	EFFECT ON EXPOSURE [a]		
	Potential Magnitude for Over-Estimation of Exposure	Potential Magnitude for Under-Estimation of Exposure	Potential Magnitude for Over- or Under Estimation of Exposure
Environmental Sampling and Analysis			
Sufficient samples may not have been taken to characterize the media being evaluated, especially with respect to currently available soil data.			Moderate
Systematic or random errors in the chemical analyses may yield erroneous data.			Low
Fate and Transport Modeling			
Chemicals in fish will be at equilibrium with chemical concentrations in water.	Low		
Use of Gaussian dispersion model to estimate air concentrations offsite.			Low
Use of a box model to estimate air concentrations onsite.	Low		
Use of Cowherd's model to estimate vehicle emission factors.		Moderate	
Exposure Parameter Estimation			
The standard assumptions regarding body weight, period exposed, life expectancy, population characteristics, and lifestyle may not be representative of any actual exposure situation.			Moderate
The amount of media intake is assumed to be constant and representative of the exposed population.	Moderate		
Assumption of daily lifetime exposure for residents.	Moderate to High		
Use of "hot spot" soil data for upper-bound lifetime exposure	Moderate to High		

[a] *As a general guideline, assumptions marked as "low", may affect estimates of exposure by less than one order of magnitude; assumptions marked "moderate" may affect estimates of exposure by between one and two orders of magnitude; assumptions marked "high" may affect estimates of exposure by more than two orders of magnitude.*

EXHIBIT 6-22

EXAMPLE OF TABLE FORMAT FOR SUMMARIZING THE RESULTS OF THE EXPOSURE ASSESSMENT -- CURRENT LAND USE [a]

Population	Exposure Pathway	Chemical	Chronic Daily Intake (CDI) (mg/kg-day)	
			Carcinogenic Effects	Noncarcinogenic Effects
Residents	Ingestion of ground water that has migrated from the site to downgradient local wells	Benzene	0.00025	-- [b]
		Chlordane	0.00015	0.00035
		Phenol	-- [c]	0.1
		Cyanide	-- [c]	0.0003
		Nitrobenzene	-- [c]	0.0001
	Inhalation of chemicals that have volatilized from ground water during use	Benzene	0.000013	-- [b]
	Ingestion of fish that have accumulated chemicals in nearby lake	Chlordane	0.00008	0.00019
		MEK	-- [c]	0.005
		Phenol	-- [c]	0.08

[a] Similar tables should be prepared for all subchronic daily intake (SDI) estimates as well as for all CDI and SDI estimates under future land use conditions.

[b] CDI for noncarcinogenic effects not calculated for benzene because it does not have an EPA-verified chronic reference dose (as of the publication date of this manual).

[c] CDI for carcinogenic effects not calculated for chemicals not considered by EPA to be potential human carcinogens (as of the publication date of this manual).

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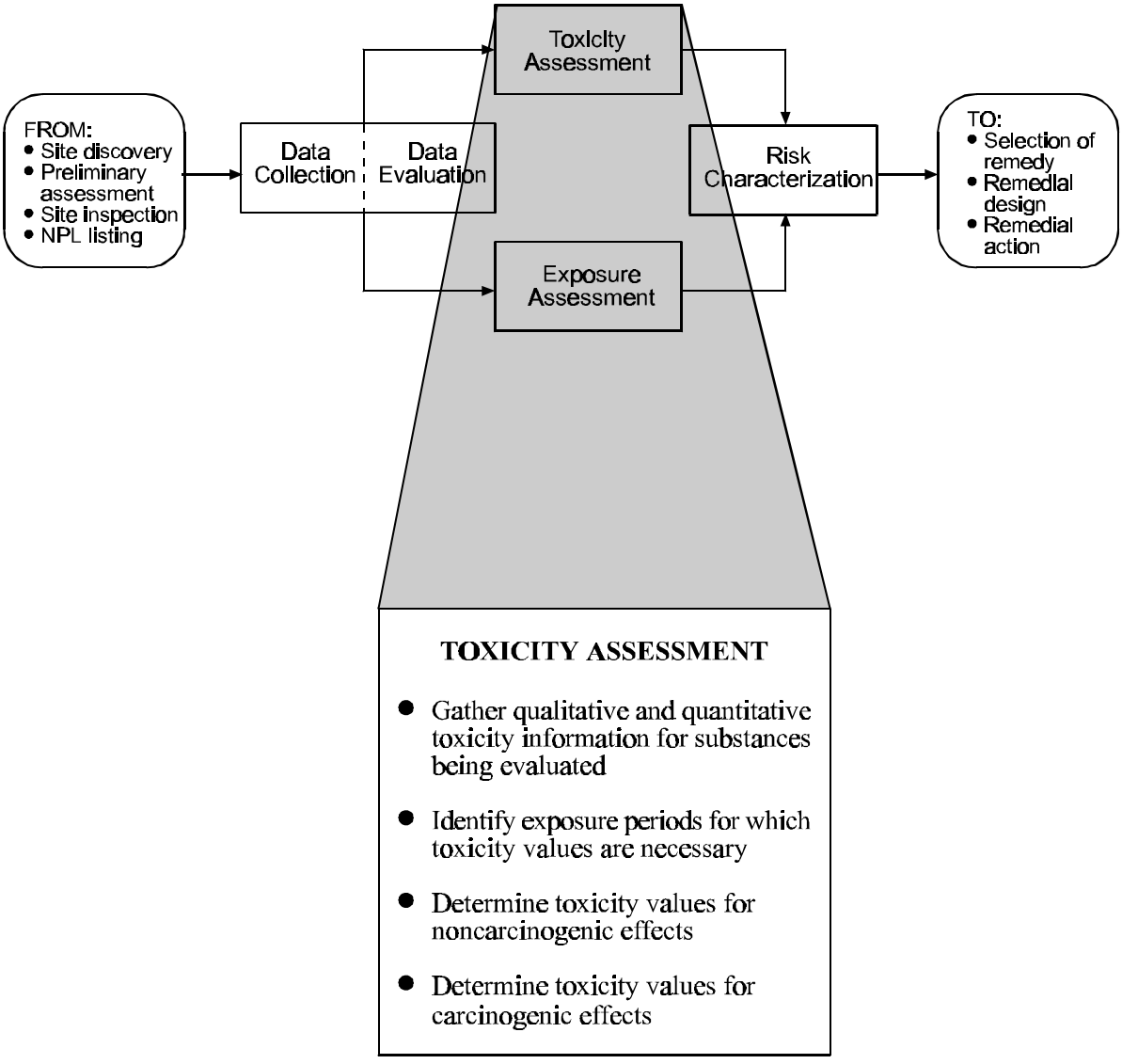
CHAPTER 7
TOXICITY ASSESSMENT



CHAPTER 7

TOXICITY ASSESSMENT

The purpose of the toxicity assessment is to weigh available evidence regarding the potential for particular contaminants to cause adverse effects in exposed individuals and to provide, where possible, an estimate of the relationship between the extent of exposure to a contaminant and the increased likelihood and/or severity of adverse effects.

Toxicity assessment for contaminants found at Superfund sites is generally accomplished in two steps: hazard identification and dose-response assessment. These two steps were first discussed in the National Academy of Sciences' publication entitled *Risk Assessment in the Federal Government - Managing the Process* and more recently in EPA's *Guidelines for Carcinogen Risk Assessment* (NAS 1983, EPA 1986). The first step, hazard identification, is the process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defect) and whether the adverse health effect is likely to occur in humans. Hazard identification involves characterizing the nature and strength of the evidence of causation. The second step, dose-response evaluation, is the process of quantitatively evaluating the toxicity information and characterizing the relationship between the dose of the contaminant administered or received and the incidence of adverse health effects in the exposed population. From this quantitative dose-response relationship, toxicity values (e.g., reference doses and slope factors) are derived that can be used to estimate the incidence or potential for adverse effects as a function of human exposure to the agent. These toxicity values are used in the risk characterization step to estimate the likelihood of adverse effects occurring in humans at different exposure levels.

Toxicity assessment is an integral part of the overall Superfund site risk assessment. Although toxicity information is critical to the risk assessment, the amount of new toxicological evaluation of primary data required to complete this step is limited in most cases. EPA has performed the toxicity assessment step for numerous chemicals and has made available the resulting toxicity information and toxicity values, which have undergone extensive peer review. At some sites, however, there will be significant data analysis and interpretation issues that should be addressed by an experienced toxicologist. This chapter provides step-by-step guidance for locating EPA toxicity assessments and accompanying values, and advises how to determine which values are most appropriate when multiple values exist. Prior to this procedural discussion, background

ACRONYMS FOR CHAPTER 7

ADI = Acceptable Daily Intake
AIC = Acceptable Intake for Chronic Exposure
AIS = Acceptable Intake for Subchronic Exposure
CRAVE = Carcinogen Risk Assessment Verification Endeavor
ECAO = Environmental Criteria and Assessment Office
HAD = Health Assessment Document
HEA = Health Effects Assessment
HEAST = Health Effects Assessment Summary Tables
HEED = Health and Environmental Effects Document
HEEP = Health and Environmental Effects Profile
IRIS = Integrated Risk Information System
LOAEL = Lowest-Observed-Adverse-Effect-Level
NOAEL = No-Observed-Adverse-Effect-Level
NOEL = No-Observed-Effect-Level
RfD = Reference Dose (when used without other modifiers, RfD generally refers to chronic reference dose)
RfD_{dt} = Developmental Reference Dose
RfD_s = Subchronic Reference Dose

DEFINITIONS FOR CHAPTER 7

Acceptable Daily Intake (ADI). An estimate similar in concept to the RfD, but derived using a less strictly defined methodology. RfDs have replaced ADIs as the Agency's preferred values for use in evaluating potential noncarcinogenic health effects resulting from exposure to a chemical.

Acceptable Intake for Chronic Exposure (AIC). An estimate similar in concept to the RfD, but derived using a less strictly defined methodology. Chronic RfDs have replaced AICs as the Agency's preferred values for use in evaluating potential noncarcinogenic health effects resulting from chronic exposure to a chemical.

Acceptable Intake for Subchronic Exposure (AIS). An estimate similar in concept to the subchronic RfD, but derived using a less strictly defined methodology. Subchronic RfDs have replaced AISs as the Agency's preferred values for use in evaluating potential noncarcinogenic health effects resulting from subchronic exposure to a chemical.

Chronic Reference Dose (RfD). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. Chronic RfDs are specifically developed to be protective for long-term exposure to a compound (as a Superfund program guideline, seven years to lifetime).

Developmental Reference Dose (RfD_{dt}). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of an exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of developmental effects. Developmental RfDs are used to evaluate the effects of a single exposure event.

Dose-response Evaluation. The process of quantitatively evaluating toxicity information and characterizing the relationship between the dose of a contaminant administered or received and the incidence of adverse health effects in the exposed population. From the quantitative dose-response relationship, toxicity values are derived that are used in the risk characterization step to estimate the likelihood of adverse effects occurring in humans at different exposure levels.

Hazard Identification. The process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defect) and whether the adverse health effect is likely to occur in humans.

Integrated Risk Information System (IRIS). An EPA data base containing verified RfDs and slope factors and up-to-date health risk and EPA regulatory information for numerous chemicals. IRIS is EPA's preferred source for toxicity information for Superfund.

Lowest-Observed-Adverse-Effect-Level (LOAEL). In dose-response experiments, the lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

No-Observed-Adverse-Effect-Level (NOAEL). In dose-response experiments, an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered to be adverse, nor precursors to specific adverse effects. In an experiment with more than one NOAEL, the regulatory focus is primarily on the highest one, leading to the common usage of the term NOAEL to mean the highest exposure level without adverse effect.

No-Observed-Effect-Level (NOEL). In dose-response experiments, an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control.

Reference Dose (RfD). The Agency's preferred toxicity value for evaluating noncarcinogenic effects resulting from exposures at Superfund sites. See specific entries for chronic RfD, subchronic RfD, and developmental RfD. The acronym RfD, when used without other modifiers, either refers generically to all types of RfDs or specifically to chronic RfDs; it never refers specifically to subchronic or developmental RfDs.

DEFINITIONS FOR CHAPTER 7
(continued)

Slope Factor. A plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime. The slope factor is used to estimate an upper-bound probability of an individual developing cancer as a result of a lifetime of exposure to a particular level of a potential carcinogen.

Subchronic Reference Dose (RfD_s). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a portion of a lifetime (as a Superfund program guideline, two weeks to seven years).

Toxicity Value. A numerical expression of a substance's dose-response relationship that is used in risk assessments. The most common toxicity values used in Superfund program risk assessments are reference doses (for noncarcinogenic effects) and slope factors (for carcinogenic effects).

Weight of Evidence Classification. An EPA classification system for characterizing the extent to which the available data indicate that an agent is a human carcinogen. Recently, EPA has developed weight-of-evidence classification systems for some other kinds of toxic effects, such as developmental effects.

information regarding EPA's methods for toxicity assessment is provided to assist the risk assessor in understanding the basis of the toxicity values and the limitations of their use. The steps of the toxicity assessment are illustrated in Exhibit 7-1.

Derivation and interpretation of toxicity values requires toxicological expertise and should not be undertaken by those without training and experience. Detailed guidance for deriving toxicity values is beyond the scope of this document. For those persons interested in obtaining additional information about EPA's methods for toxicity assessment, references to appropriate guidance documents are given throughout this chapter.

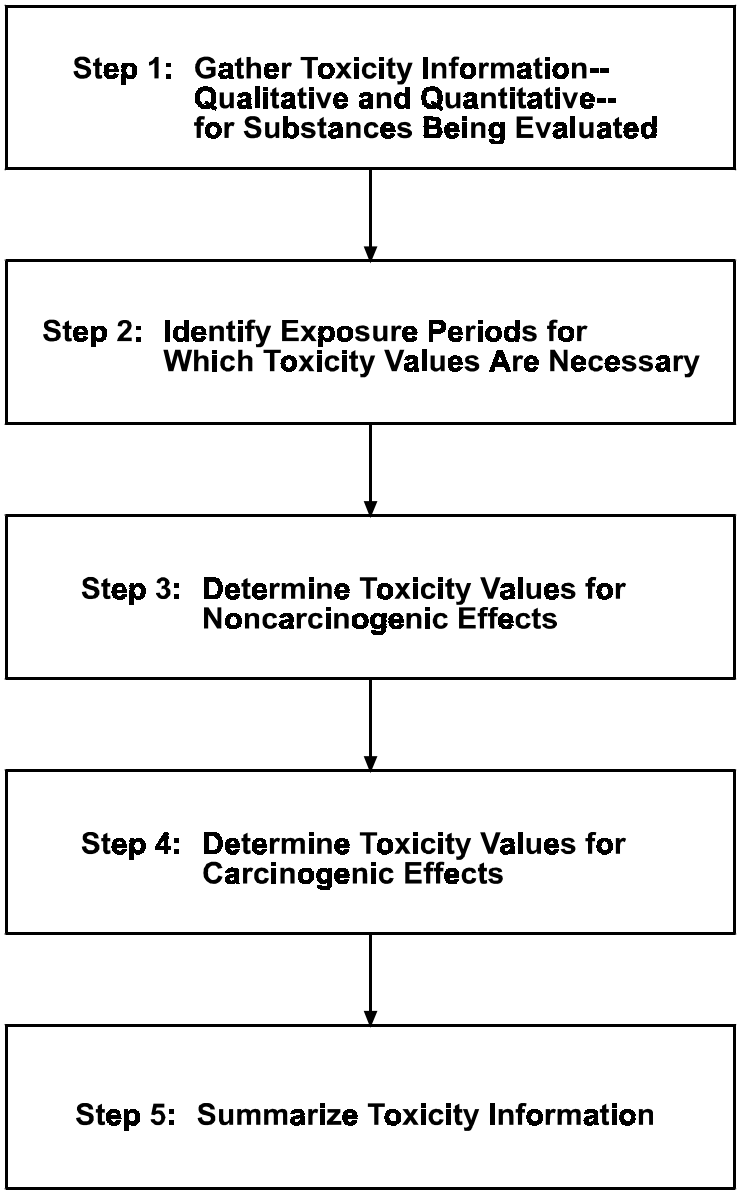
7.1 TYPES OF TOXICOLOGICAL INFORMATION CONSIDERED IN TOXICITY ASSESSMENT

This section summarizes information from several EPA documents (especially EPA 1989a, f) on the basic types of data used in toxicity assessment. As part of the hazard identification step of the toxicity assessment, EPA gathers evidence from a variety of sources regarding the potential for a contaminant to cause adverse health effects (carcinogenic and noncarcinogenic) in humans. These sources may include controlled epidemiologic investigations, clinical studies, and experimental animal studies. Supporting information may be obtained from sources such as *in vitro* test results and comparisons of structure-activity relationships.

7.1.1 HUMAN DATA

Well-conducted epidemiologic studies that show a positive association between an agent and a disease are accepted as the most convincing evidence about human risk. At present, however, human data adequate to serve as the sole basis of a dose-response assessment are available for only a few chemicals. Humans are generally exposed in the workplace or by accident, and because these types of exposures are not intentional, the circumstances of the exposures (concentration and time) may not be well known. Often the incidence of effects is low, the number of exposed individuals is small, the latent period between exposure and disease is long, and exposures are to mixed and multiple substances. Exposed populations may be heterogeneous, varying in age, sex, genetic constitution, diet, occupational and home environment, activity patterns, and other cultural factors affecting susceptibility. For these reasons, epidemiologic data require careful interpretation. If adequate human studies (confirmed for validity and applicability) exist, these studies are given first priority in the dose-response assessment, and animal toxicity studies are used as supportive evidence.

EXHIBIT 7-1
STEPS IN TOXICITY ASSESSMENT



Human studies having inadequate exposure-response information for a quantitative assessment are often used as supporting data. Such studies may establish a qualitative relationship between environmental exposures and the presence of an adverse effect in exposed human populations. For example, case reports of exposures resulting in effects similar to the types of effects observed in animals provide support for the conclusions drawn from the animal data.

7.1.2 ANIMAL DATA

The toxicity data base for most chemicals lacks sufficient information on toxic effects in humans. In such cases, EPA may infer the potential for the substance to cause an adverse effect in humans from toxicity information drawn from experiments conducted on non-human mammals, such as the rat, mouse, rabbit, guinea pig, hamster, dog, or monkey. The inference that humans and animals (mammals) are similar, on average, in intrinsic susceptibility to toxic chemicals and that data from animals can in many cases be used as a surrogate for data from humans is the basic premise of modern toxicology. This concept is particularly important in the regulation of toxic chemicals. There are occasions, however, in which observations in animals may be of uncertain relevance to humans. EPA considers the likelihood that the agent will have adverse effects in humans to increase as similar results are observed across sexes, strains, species, and routes of exposure in animal studies.

7.1.3 SUPPORTING DATA

Several other types of studies used to support conclusions about the likelihood of occurrence of adverse health effects in humans are described below. At the present time, EPA considers all of these types of data to be supportive, not definitive, in assessing the potential for adverse health effects in humans.

Metabolic and other pharmacokinetic studies may be used to provide insights into the mechanism of action of a particular compound. By comparing the metabolism of a compound exhibiting a toxic effect in an animal with the corresponding metabolism in humans, evidence for the potential of the compound to have toxic effects in humans may be obtained.

Studies using cell cultures or microorganisms may be used to provide insights into a compound's potential for biological activity. For example, tests for point mutations, numerical and structural chromosome aberrations, DNA damage/repair, and cell transformation may provide supportive evidence of carcinogenicity and may give information on potential mechanisms of carcinogenicity. It should be noted, however, that lack of positive results in short-term tests for genotoxicity is not considered a basis for discounting positive results in long-term carcinogenicity studies in animals.

Structure-activity studies (i.e., predictions of toxicologic activity based on analysis of chemical structure) are another potential source of supporting data. Under certain circumstances, the known activity of one compound may be used to estimate the activity of another structurally related compound for which specific data are lacking.

7.2 TOXICITY ASSESSMENT FOR NONCARCINOGENIC EFFECTS

This section summarizes how the types of toxicity information presented in Section 7.1 are considered in the toxicity assessment for noncarcinogenic effects. A reference dose, or RfD, is the toxicity value used most often in evaluating noncarcinogenic effects resulting from exposures at Superfund sites. Additionally, One-day or Ten-day Health Advisories (HAs) may be used to evaluate short-term oral exposures. The methods EPA uses for developing RfDs and HAs are described below. Various types of RfDs are available depending on the exposure route (oral or inhalation), the critical effect (developmental or other), and the length of exposure being evaluated (chronic, subchronic, or single event). This section is intended to be a summary description only; for additional details, refer to the appropriate guidelines and other sources listed as references for this chapter (especially EPA 1986b, EPA 1989b-f).

A chronic RfD is defined as an estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that

is likely to be without an appreciable risk of deleterious effects during a lifetime. Chronic RfDs are specifically developed to be protective for long-term exposure to a compound. As a guideline for Superfund program risk assessments, chronic RfDs generally should be used to evaluate the potential noncarcinogenic effects associated with exposure periods between 7 years (approximately 10 percent of a human lifetime) and a lifetime. Many chronic RfDs have been reviewed and verified by an intra-Agency RfD Workgroup and entered into the Agency's Integrated Risk Information System (IRIS).

FORMER TERMINOLOGY

Prior to the development of RfDs, noncarcinogenic effects of chronic exposures were evaluated using values called acceptable daily intakes (ADIs) or acceptable intakes for chronic exposure (AICs). While ADIs and AICs are similar in concept to RfDs, RfDs have been derived using a more strictly defined methodology and represent the Agency's preferred toxicity values. Furthermore, many chronic RfDs have been reviewed and verified by an intra-Agency RfD Workgroup; these verified RfDs represent an Agency consensus and are preferred over other RfDs that have not undergone such review (see Section 7.2.7, Verification of RfDs). Similarly, acceptable intakes for subchronic exposures (AISs) have been superseded by the more strictly defined subchronic RfD values. Therefore, the former terminology (ADI, AIC, AIS) should no longer be used in Superfund program risk assessments.

More recently, EPA has begun developing subchronic RfDs (RfD_ss), which are useful for characterizing potential noncarcinogenic effects associated with shorter-term exposures, and developmental RfDs (RfD_{dt}s), which are useful specifically for assessing potential developmental effects resulting from exposure to a compound. As a guideline for Superfund program risk assessments, subchronic RfDs should be used to evaluate the potential noncarcinogenic effects of exposure periods between two weeks and seven years. Such short-term exposures can result when a particular activity is performed for a limited number of years or when a chemical with a short half-life degrades to negligible concentrations within several months. Developmental RfDs are used to evaluate the potential effects on a developing organism following a single exposure event.

7.2.1 CONCEPT OF THRESHOLD

For many noncarcinogenic effects, protective mechanisms are believed to exist that must be overcome before the adverse effect is manifested. For example, where a large number of cells perform the same or similar function, the cell population may have to be significantly depleted before the effect is seen. As a result, a range of exposures exists from zero to some finite value that can be tolerated by the organism with essentially no chance of expression of adverse effects. In developing a toxicity value for evaluating noncarcinogenic effects (i.e., an RfD), the approach is to identify the upper bound of this tolerance range (i.e., the maximum subthreshold level). Because variability exists in the human population, attempts are made to identify a subthreshold level protective of sensitive individuals in the population. For most chemicals, this level can only be estimated; the RfD incorporates uncertainty factors indicating the degree or extrapolation used to derive the estimated value. RfD summaries in IRIS also contain a statement expressing the overall confidence that the evaluators have in the RfD (high, medium, or low). The RfD is generally considered to have uncertainty spanning an order of magnitude or more, and therefore the RfD should not be viewed as a strict scientific demarcation between what level is toxic and nontoxic.

7.2.2 DERIVATION OF AN ORAL RfD (RfD_o)

Identifying the critical study and determining the NOAEL. In the development of oral RfDs, all available studies examining the toxicity of a chemical following exposure by the oral route are gathered and judged for scientific merit. Occasionally, studies based on other exposure routes (e.g., inhalation) are considered, and the data are adjusted for application to the oral route. Any differences between studies are reconciled and an overall evaluation is reached. If adequate human data are available, this information is used as the basis of the RfD. Otherwise, animal study data are used; in these cases, a series of professional judgments are made that involve, among other considerations, an assessment of the relevance and scientific quality of the experimental studies. If data from several animal studies are being evaluated, EPA first seeks to identify the animal model that is most relevant to humans based on a defensible

biological rationale, for instance, using comparative metabolic and pharmacokinetic data. In the absence of a species that is clearly the most relevant, EPA assumes that humans are at least as sensitive to the substance as the most sensitive animal species tested. Therefore, as a matter of science policy, the study on the most sensitive species (the species showing a toxic effect at the lowest administered dose) is selected as the critical study for the basis of the RfD. The effect characterized by the "lowest-observed-adverse-effect-level" (LOAEL) after dosimetric conversions to adjust for species differences is referred to as the critical toxic effect.

After the critical study and toxic effect have been selected, EPA identifies the experimental exposure level representing the highest level tested at which no adverse effects (including the critical toxic effect) were demonstrated. This highest "no-observed-adverse-effect level" (NOAEL) is the key datum obtained from the study of the dose-response relationship. A NOAEL observed in an animal study in which the exposure was intermittent (such as five days per week) is adjusted to reflect continuous exposure.

The NOAEL is selected based in part on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented. The NOAEL for the critical toxic effect should not be confused with the "no-observed-effect level" (NOEL). The NOEL corresponds to the exposure level at which no effect at all has been observed; frequently, effects are observed that are not considered to be of toxicological significance. In some studies, only LOAEL rather than a NOAEL is available. The use of a LOAEL, however, requires the use of an additional uncertainty factor (see below).

MULTIPLE TOXIC EFFECTS AND RfDs

The RfD is developed from a NOAEL for the most sensitive, or critical, toxic effect based in part on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented. It should be remembered during the risk characterization step of the risk assessment that if exposure levels exceed the RfD, then adverse effects in addition to the critical toxic effect may begin to appear.

Applying uncertainty factors. The RfD is derived from the NOAEL (or LOAEL) for the critical toxic effect by consistent application of uncertainty factors (UFs) and a modifying factor (MF). The uncertainty factors generally consist of multiples of 10 (although values less than 10 are sometimes used), with each factor representing a specific area of uncertainty inherent in the extrapolation from the available data. The bases for application of different uncertainty factors are explained below.

- A UF of 10 is used to account for variation in the general population and is intended to protect sensitive subpopulations (e.g., elderly, children).

- A UF of 10 is used when extrapolating from animals to humans. This factor is intended to account for the interspecies variability between humans and other mammals.

- A UF of 10 is used when a NOAEL derived from a subchronic instead of a chronic study is used as the basis for a chronic RfD.

- A UF of 10 is used when a LOAEL is used instead of a NOAEL. This factor is intended to account for the uncertainty associated with extrapolating from LOAELs to NOAELs.

In addition to the UFs listed above, a modifying factor (MF) is applied.

- An MF ranging from >0 to 10 is included to reflect a qualitative professional assessment of additional uncertainties in the critical study and in the entire data base for the chemical not explicitly addressed by the preceding uncertainty factors. The default value for the MF is 1.[1]

To calculate the RfD, the appropriate NOAEL (or the LOAEL if a suitable NOAEL is not available) is divided by the product of all of the applicable uncertainty factors and the modifying factor. That is:

$$RfD = NOAEL \text{ or } LOAEL/(UF_1 \times UF_2 \ldots \times$$

MF)

Oral RfDs typically are expressed as one significant figure in units of mg/kg-day. These concepts are shown graphically in EPA (1989g). To date, most RfDs developed by EPA and included in the sources listed in Section 7.4 are based on administered doses, not absorbed doses (see box on page 7-10).

7.2.3 DERIVATION OF AN INHALATION RfD (RfD_i)

The methods EPA uses in the derivation of inhalation RfDs are similar in concept to those used for oral RfDs; however, the actual analysis of inhalation exposures is more complex than oral exposures due to (1) the dynamics of the respiratory system and its diversity across species and (2) differences in the physicochemical properties of contaminants. Additional information can be found in EPA's *Interim Methods for Development of Inhalation Reference Doses* (EPA 1989d).

Identifying the critical study and determining the NOAEL. Although in theory the identification of the critical study and the determination of the NOAEL is similar for oral and inhalation exposures, several important differences should be noted. In selecting the most appropriate study, EPA considers differences in respiratory anatomy and physiology, as well as differences in the physicochemical characteristics of the contaminant. Differences in respiratory anatomy and physiology may affect the pattern of contaminant deposition in the respiratory tract, and the clearance and redistribution of the agent. Consequently, the different species may not receive the same dose of the contaminant at the same locations within the respiratory tract even though both species were exposed to the same particle or gas concentration. Differences in the physicochemical characteristics of the contaminants, such as the size and shape of a particle or whether the contaminant is an aerosol or a gas, also influence deposition, clearance, and redistribution.

In inhalation exposures, the target tissue may be a portion of the respiratory tract or, if the contaminant can be absorbed and distributed through the body, some extrarespiratory organ. Because the pattern of deposition may influence concentrations at the alveolar exchange boundary or different tissues of the lung, the toxic health effect observed may be more directly related to the pattern of deposition than to the exposure concentration. Consequently, EPA considers the deposition, clearance mechanisms, and the physicochemical properties of the inhaled agent in determining the effective dose delivered to the target organ.

Doses calculated in animals are converted to equivalent doses in humans on the basis of comparative physiological considerations (e.g., ventilatory parameters, regional lung surface areas). Additionally, if the exposure period was discontinuous, it is adjusted to reflect continuous exposure.

Applying uncertainty factors. The inhalation RfD is derived from the NOAEL by applying uncertainty factors similar to those listed above for oral RfDs. The UF of 10 is used when extrapolating from animals to humans, in addition to calculation of the human equivalent dose, to account for interspecific variability in sensitivity to the toxicant. The resulting RfD value for inhalation exposure is generally reported as a concentration in air (in mg/m^3 for continuous, 24 hour/day exposure), although it may be reported as a corresponding inhaled intake (in mg/kg-day). A human body weight of 70 kg and an inhalation rate of 20 m^3/day are used to convert between an inhaled intake expressed in units of mg/kg-day and a concentration in air expressed in mg/m^3.

7.2.4 DERIVATION OF A SUBCHRONIC RfD (RfD_s)

The chronic RfDs described above pertain to lifetime or other long-term exposures and may be overly protective if used to evaluate the potential for adverse health effects resulting from substantially less-than-lifetime exposures. For such situations, EPA has begun calculating toxicity values specifically for subchronic exposure durations, using a method similar to that outlined above for chronic RfDs. EPA's Environmental Criteria and Assessment Office develops subchronic RfDs and, although they have been peer-reviewed by Agency and outside reviewers, RfDs values have not undergone verification by an intra-Agency workgroup (see Section 7.2.7). As a result,

subchronic RfDs are considered interim rather than verified toxicity values and are not placed in IRIS.

Development of subchronic reference doses parallels the development of chronic reference doses in concept; the distinction is one of exposure duration. Appropriate studies are evaluated and a subchronic NOAEL is identified. The RfD_s is derived from the NOAEL by the application of UFs and MF as outlined above. When experimental data are available only for shorter exposure durations than desired, an additional uncertainty factor is applied. This is similar to the application of the uncertainty factor for duration differences when a chronic RfD is estimated from subchronic animal data. On the other hand, if subchronic data are missing and a chronic oral RfD derived from chronic data exists, the chronic oral RfD is adopted as the subchronic oral RfD. There is no application of an uncertainty factor to account for differences in exposure duration in this instance.

7.2.5 DERIVATION OF DEVELOPMENTAL TOXICANT RfD (RfD_{dt})

In developing an RfD_{dt}, evidence is gathered regarding the potential of a substance to cause adverse effects in a developing organism as a result of exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse effects can include death, structural abnormality, altered growth, and functional deficiencies. Maternal toxicity also is considered. The evidence is assessed, and the substance is assigned a weight-of-evidence designation according to the scheme outlined below and summarized in the box in the opposite column. In this scheme, three levels are used to indicate the assessor's degree of confidence in the data: definitive evidence, adequate evidence, and inadequate evidence. The definitive and adequate evidence categories are subdivided as to whether the evidence demonstrates the occurrence or the absence of adverse effects.

WEIGHT-OF-EVIDENCE SCHEME FOR DEVELOPMENTAL TOXICITY

- Definitive Evidence for:
  - Human Developmental Toxicity
  - No Apparent Human Developmental Toxicity
- Adequate Evidence for:
  - Potential Human Developmental Toxicity
  - No Apparent Potential Human Developmental Toxicity
- Inadequate Evidence for Determining Potential Human Developmental Toxicity

After the weight-of-evidence designation is assigned, a study is selected for the identification of a NOAEL. The NOAEL is converted to an equivalent human dose, if necessary, and divided by uncertainty factors similar to those used in the development of an oral RfD. It should be remembered that the RfD_{dt} is based on a short duration of exposure because even a single exposure at a critical time (e.g., during gestation) may be sufficient to produce adverse developmental effects and that chronic exposure is not a prerequisite for developmental toxicity to be manifested. Therefore, RfD_{dt} values are appropriate for evaluating single event exposures, which usually are not adjusted based on the duration of exposure. Additional information on the derivation of RfD_{dt} values is available in EPA's *Proposed Amendments to the Guidelines for the Health Assessment of Suspect Developmental Toxicants* (EPA 1989e).

7.2.6 ONE-DAY AND TEN-DAY HEALTH ADVISORIES

Reference values that may be useful for evaluating potential adverse effects associated with oral exposures of shorter duration have been developed by the Office of Drinking Water. These values are known as One-day and Ten-day Health Advisories, which are issued as nonregulatory guidance. Health Advisory values are concentrations of contaminants in drinking water at which adverse health effects would not be expected to occur for an

exposure of the specified duration. The Health Advisory values are based on data describing noncarcinogenic effects and are derived by dividing a NOAEL or LOAEL by the appropriate uncertainty and modifying factors. They are based on a 10-kg child assumed to drink 1 liter of water per day, and a margin of safety is included to protect sensitive members of the population. One-day and Ten-day Health Advisories do not consider any carcinogenic risk associated with the exposure even if the compound is a potential carcinogen. For additional information on the derivation of Health Advisory values, refer to the Agency's guidance document (EPA 1989c).

7.2.7 VERIFICATION OF RfDs

EPA has formed an RfD Workgroup composed of members from many EPA offices to verify existing Agency RfDs and to resolve conflicting toxicity assessments and toxicity values within the Agency. The Workgroup reviews the information regarding the derivation of an RfD for a substance and summarizes its evaluations, conclusions, and reservations regarding the RfD in a standardized summary form from one to several pages in length. This form contains information regarding the development of the RfD, such as the chosen effect levels and uncertainty factors, as well as a statement on the confidence that the evaluators have in the RfD itself, the critical study, and the overall data base (high, medium, or low). Once verified, these data evaluation summaries are entered into IRIS and are available for public access.

Workgroup-approved RfDs are referred to as verified RfDs. Those RfDs awaiting workgroup approval are referred to as interim RfDs. At the time of this manual's publication, only chronic RfDs are being verified. No workgroup has been established to verify subchronic RfDs or developmental RfDs.

ABSORBED VERSUS ADMINISTERED DOSE

Toxicity values -- for both noncarcinogenic and carcinogenic effects -- are generally calculated from critical effect levels based on administered rather than absorbed doses. It is important, therefore, to compare such toxicity values to exposure estimates expressed as intakes (corresponding to administered doses), not as absorbed doses. For the few toxicity values that have been based on absorbed doses, either the exposure estimate or the toxicity value should be adjusted to make the values comparable (i.e., compare exposures estimated as absorbed doses to toxicity values expressed as absorbed doses, and exposures estimated as intakes to toxicity values expressed as administered doses). See Appendix A for guidance on making adjustments for absorption efficiency.

7.3 TOXICITY ASSESSMENT FOR CARCINOGENIC EFFECTS

This section describes how the types of toxicity information presented in Section 7.1 are considered in the toxicity assessment for carcinogenic effects. A slope factor and the accompanying weight-of-evidence determination are the toxicity data most commonly used to evaluate potential human carcinogenic risks. The methods EPA uses to derive these values are outlined below. Additional information can be obtained by consulting EPA's *Guidelines for Carcinogen Risk Assessment* (EPA 1986a) and Appendix B to IRIS (EPA 1989a).

7.3.1 CONCEPT OF NONTHRESHOLD EFFECTS

Carcinogenesis, unlike many noncarcinogenic health effects, is generally thought to be a phenomenon for which risk evaluation based on

presumption of a threshold is inappropriate. For carcinogens, EPA assumes that a small number of molecular events can evoke changes in a single cell that can lead to uncontrolled cellular proliferation and eventually to a clinical state of disease. This hypothesized mechanism for carcinogenesis is referred to as "nonthreshold" because there is believed to be essentially no level of exposure to such a chemical that does not pose a finite probability, however small, of generating a carcinogenic response. That is, no dose is thought to be risk-free. Therefore, in evaluating cancer risks, an effect threshold cannot be estimated. For carcinogenic effects, EPA uses a two-part evaluation in which the substance first is assigned a weight-of-evidence classification, and then a slope factor is calculated.

7.3.2 ASSIGNING A WEIGHT OF EVIDENCE

In the first step of the evaluation, the available data are evaluated to determine the likelihood that the agent is a human carcinogen. The evidence is characterized separately for human studies and animal studies as sufficient, limited, inadequate, no data, or evidence of no effect. The characterizations of these two types of data are combined, and based on the extent to which the agent has been shown to be a carcinogen in experimental animals or humans, or both, the agent is given a provisional weight-of-evidence classification. EPA scientists then adjust the provisional classification upward or downward, based on other supporting evidence of carcinogenicity (see Section 7.1.3). For a further description of the role of supporting evidence, see the EPA guidelines (EPA 1986a).

The EPA classification system for weight of evidence is shown in the box in the opposite column. This system is adapted from the approach taken by the International Agency for Research on Cancer (IARC 1982).

7.3.3 GENERATING A SLOPE FACTOR[2]

In the second part of the evaluation, based on the evaluation that the chemical is a known or probable human carcinogen, a toxicity value that defines quantitatively the relationship between dose and response (i.e., the slope factor) is calculated. Slope factors are typically calculated for potential carcinogens in classes A, B1, and B2. Quantitative estimation of slope factors for the chemicals in class C proceeds on a case-by-case basis.

Generally, the slope factor is a plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime. The slope factor is used in risk assessments to estimate an upper-bound lifetime probability of an individual developing cancer as a result of exposure to a particular level of a potential carcinogen. Slope factors should always be accompanied by the weight-of-evidence classification to indicate the strength of the evidence that the agent is a human carcinogen.

Identifying the appropriate data set. In deriving slope factors, the available information about a chemical is evaluated and an appropriate data set is selected. In choosing appropriate data sets, human data of high quality are preferable to animal data. If animal data are used, the species that responds most similarly to humans (with respect to factors such as metabolism, physiology, and pharmacokinetics) is preferred. When no clear choice is possible, the most sensitive species is given the greatest emphasis. Occasionally, in situations where no single study is judged most appropriate, yet several studies collectively support the estimate, the geometric mean

EPA WEIGHT-OF-EVIDENCE CLASSIFICATION SYSTEM FOR CARCINOGENICITY

Group	Description
A	Human carcinogen
B1 or B2	Probable human carcinogen
	B1 indicates that limited human data are available.
	B2 indicates sufficient evidence in animals and inadequate or no evidence in humans.
C	Possible human carcinogen
D	Not classifiable as to human carcinogenicity
E	Evidence of noncarcinogenicity for humans

of estimates from all studies may be adopted as the slope. This practice ensures the inclusion of all relevant data.

Extrapolating to lower doses. Because risk at low exposure levels is difficult to measure directly either by animal experiments or by epidemiologic studies, the development of a slope factor generally entails applying a model to the available data set and using the model to extrapolate from the relatively high doses administered to experimental animals (or the exposures noted in epidemiologic studies) to the lower exposure levels expected for human contact in the environment.

A number of mathematical models and procedures have been developed to extrapolate from carcinogenic responses observed at high doses to responses expected at low doses. Different extrapolation methods may provide a reasonable fit to the observed data but may lead to large differences in the projected risk at low doses. In keeping with EPA's *Guidelines for Carcinogen Risk Assessment* (EPA 1986a) and the principles outlined in *Chemical Carcinogens: A Review of the Science and Its Associated Principles* (OSTP 1985), the choice of a low-dose extrapolation model is governed by consistency with current understanding of the mechanism of carcinogenesis, and not solely on goodness-of-fit to the observed tumor data. When data are limited and when uncertainty exists regarding the mechanisms of carcinogenic action, the EPA guidelines and OSTP principles suggest that models or procedures that incorporate low-dose linearity are preferred when compatible with the limited information available. EPA's guidelines recommend that the linearized multistage model be employed in the absence of adequate information to the contrary. Among the other models available are the Weibull, probit, logit, one-hit, and gamma multihit models, as well as various time-to-tumor models. Most of these models are less conservative (i.e., predict lower cancer potency) than the linearized multistage model. These concepts and models are shown graphically in EPA (1989g) and OTA (1981).

In general, after the data are fit to the appropriate model, the upper 95th percent confidence limit of the slope of the resulting dose-response curve is calculated. This value is known as the slope factor and represents an upper 95th percent confidence limit on the probability of a response per unit intake of a chemical over a lifetime (i.e., there is only a 5 percent chance that the probability of a response could be greater than the estimated value on the basis of the experimental data and model used). In some cases, slope factors based on human dose-response data are based on the "best" estimate instead of the upper 95th percent confidence limits. Because the dose-response curve generally is linear only in the low-dose region, the slope factor estimate only holds true for low doses. Information concerning the limitations on use of slope factors can be found in IRIS.

Determining equivalent human doses. When animal data are used as a basis for extrapolation, the human dose that is equivalent to the dose in the animal study is calculated using the assumption that different species are equally sensitive to the effects of a toxicant if they absorb the same amount of the agent (in milligrams) per unit of body surface area. This assumption is made only in the absence of specific information about the equivalent doses for the chemical in question. Because surface area is approximately proportional to the 2/3 power of body weight, the equivalent human dose (in mg/day, or other units of mass per unit time) is calculated by multiplying the animal dose (in identical units) by the ratio of human to animal body weights raised to the 2/3 power. (For animal doses expressed as mg/kg-day, the equivalent human dose, in the same units, is calculated by multiplying the animal dose by the ratio of animal to human body weights raised to the 1/3 power.)

When using animal inhalation experiments to estimate lifetime human risks for partially soluble vapors or gases, the air concentration (ppm) is generally considered to be the equivalent dose between species based on equivalent exposure times (measured as fractions of a lifetime). For inhalation of particulates or completely absorbed gases, the amount absorbed per unit of body surface area is considered to be the equivalent dose between species.

Summary of dose-response parameters. Toxicity values for carcinogenic effects can be expressed in several ways. The slope factor is usually, but not always, the upper 95th percent confidence limit of the slope of the dose-response curve and is expressed as

$(mg/kg\text{-}day)^{-1}$. If the extrapolation model selected is the linearized multistage model, this value is also known as the q_1^*. That is:

Slope factor = risk per unit dose
= risk per mg/kg-day

Where data permit, slope factors listed in IRIS are based on absorbed doses, although to date many of them have been based on administered doses. (The qualifiers related to absorbed versus administered dose given in the box on page 7-10 apply to assessment of cancer risk as well as to assessment of potential noncarcinogenic effects.)

Toxicity values for carcinogenic effects also can be expressed in terms of risk per unit concentration of the substance in the medium where human contact occurs. These measures, called unit risks, are calculated by dividing the slope factor by 70 kg and multiplying by the inhalation rate (20 m^3/day) or the water consumption rate (2 liters/day), respectively, for risk associated with unit concentration in air or water. Where an absorption fraction less than 1.0 has been applied in deriving the slope factor, an additional conversion factor is necessary in the calculation of unit risk so that the unit risk will be on an administered dose basis. The standardized duration assumption for unit risks is understood to be continuous lifetime exposure. Hence, when there is no absorption conversion required:

air unit risk = risk per ug/m^3
= slope factor x 1/70 kg x $20m^3$/day x 10^{-3}

water unit risk = risk per ug/L
= slope factor x 1/70 kg x 2L/day x 10^{-3}

The multiplication by 10^{-3} is necessary to convert from mg (the slope factor, or q_1^*, is given in $(mg/kg\text{-}day)^{-1}$) to ug (the unit risk is given in $(ug/m^3)^{-1}$ or $(ug/L)^{-1}$).

7.3.4 VERIFICATION OF SLOPE FACTORS

EPA formed the Carcinogen Risk Assessment Verification Endeavor (CRAVE) Workgroup to validate Agency carcinogen risk assessments and resolve conflicting toxicity values developed by various program offices. Workgroup members represent many different EPA offices and are scientists experienced in issues related to both the qualitative and quantitative risk assessment of carcinogenic agents. Slope factors verified by CRAVE have undergone extensive peer review and represent an Agency consensus. CRAVE- verified review summaries (similar to RfD Workgroup summaries) are entered into the IRIS data base.

7.4 IDENTIFYING APPROPRIATE TOXICITY VALUES FOR SITE RISK ASSESSMENT

Using the methods outlined above, EPA has performed toxicity assessments for many chemicals found at Superfund sites and has made the results available for use. This section provides step-by-step methods for locating appropriate toxicity information, including numerical toxicity values, to be used in Superfund risk assessments. Because one's confidence in toxicity values depends heavily on the data base and the methods of extrapolation used in their development, guidance is also included for identifying the important information on which these values are based.

7.4.1 GATHER TOXICITY INFORMATION FOR CHEMICALS BEING EVALUATED

In the first step of the toxicity assessment, information is collected regarding the toxic effects that occur following exposure to the chemical being evaluated. Particular attention should be paid to the route of exposure, the frequency and length of exposure, and the doses at which the adverse effects are expected to occur. Chemicals having potential reproductive or developmental effects should be flagged. Later in the evaluation, special reference doses for developmental effects can be sought for these chemicals.

Several sources may provide useful toxicity information and references to primary literature, although only some of them should be used as sources for slope factors and reference doses (as explained below).

Integrated Risk Information System (IRIS).[3] IRIS is an EPA data base containing up-to-date health risk and EPA regulatory information for numerous chemicals. IRIS contains only those RfDs and slope factors that have been verified by the RfD or CRAVE Workgroups and consequently, is considered to be the preferred source of toxicity information. Information in IRIS supersedes all other sources. Only if information is not available in IRIS for the chemical being evaluated should the sources below be consulted. IRIS consists of a collection of computer files on individual chemicals. Existing information on the chemicals is updated as new scientific data are reviewed. New files and new chemicals are added as information becomes available. These chemical files contain descriptive and quantitative information in the following categories:

- oral and inhalation chronic reference doses;
- oral and inhalation slope factors and unit risks for chronic exposure to carcinogens;
- Health Advisories from EPA's Office of Drinking Water;
- EPA regulatory action summaries; and
- supplemental data on acute health hazards and physical/chemical properties.

To ensure access to the most up-to-date chemical information, IRIS is only available on-line. For information on how to access this data base, call IRIS User Support at 513-569-7254 or see the *Federal Register* notice regarding the availability of IRIS (EPA 1988a).

Should EPA regional staff have specific technical or scientific questions about any verification workgroup's analysis of particular data cited in IRIS, the Agency contact for a particular chemical (identified at the end of each IRIS file) should be consulted. If new data are identified suggesting that existing IRIS information may be outdated, or if there is concern or disagreement about the overall findings of particular files, the Agency IRIS coordinator should be consulted. The IRIS coordinator can assist in making arrangements should discussions with a verification workgroup be needed.

Health Effects Assessment Summary Tables (HEAST). Formerly "The Quarterly" and associated references, HEAST is a tabular presentation of toxicity information and values for chemicals for which Health Effects Assessments (HEAs), Health and Environmental Effects Documents (HEEDs), Health and Environmental Effects Profiles (HEEPs), Health Assessment Documents (HADs), or Ambient Air Quality Criteria Documents (AAQCDs) have been prepared. HEAST summarizes interim (and some verified) RfDs and slope factors as well as other toxicity information for specific chemicals. In addition, HEAST directs readers to the most current sources of supporting toxicity information through an extensive reference section. Therefore, HEAST is especially helpful when verified information for a chemical is not in IRIS. HEAST, which is updated quarterly, also provides a valuable pointer system for identifying current references on chemicals that are not in IRIS.

HEAST can be obtained upon request from the Superfund Docket (FTS or 202-382-3046). The Docket will mail copies of HEAST to callers and place requestors on a mailing list to receive an updated version quarterly. HEAs, HEEDs, HEEPs, HADs, and AAQCDs referenced in HEAST are available through EPA's Center for Environmental Research Information (CERI) in Cincinnati, OH (513-569-7562 or FTS 684-7562) or the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650 or 800-336-4700).

EPA criteria documents. These documents include drinking water criteria documents, drinking water Health Advisory summaries, ambient water quality

HIERARCHY OF TOXICITY INFORMATION

Because toxicity information may change rapidly and quickly become outdated, care should be taken to find the most recent information available. IRIS is updated monthly, provides verified RfDs and slope factors, and is the Agency's preferred source of toxicity information. Only if values are unavailable in IRIS should other information sources be consulted.

HEAST is the second most current source of toxicity information of importance to Superfund. Unlike IRIS, HEAST provides information regarding interim as well as verified RfDs and slope factors. Readers are directed to supporting toxicity information for interim and verified values in an extensive reference section of HEAST. HEAST information should only be sought for those chemicals not listed in IRIS.

Toxicity information, RfDs, and slope factors also can be found in other EPA documents. Although these values were developed by offices within the Agency, they have not necessarily been verified by the RfD or CRAVE Workgroups. The use of up-to-date verified information is preferred to the use of interim information and, therefore, toxicity information should be obtained from other EPA references only if information could not be found in IRIS or HEAST. Before using references other than those cited in IRIS or HEAST, check with ECAO at 513-569-7300 (FTS 684-7300) to see if more current information is available.

criteria documents, and air quality criteria documents, and contain general toxicity information that can be used if information for a chemical is not available through IRIS or the HEAST references. Criteria documents are available through NTIS at the address given above. Information on drinking water criteria documents can be obtained through the Safe Drinking Water Hotline (800-426-4791).

Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles. ATSDR is developing toxicological profiles for 275 hazardous substances found at Superfund sites. The first 200 substances to be addressed have been identified in *Federal Register* notices (EPA 1987, 1988b). These profiles contain general toxicity information and levels of exposure associated with lethality, cancer, genotoxicity, neurotoxicity, developmental and reproductive toxicity, immunotoxicity, and systemic toxicity (i.e., hepatic, renal, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, and dermal/ocular effects). Health effects in humans and animals are discussed by exposure route (i.e., oral, inhalation, and dermal) and duration (i.e., acute, intermediate, and chronic). Also included in the profiles are chapters on physicochemical properties, environmental fate, potential for human exposure, analytical methods, and regulatory and advisory status. Contact NTIS at the address given on the previous page for further information on the status or availability of a particular profile.

EPA's Environmental Criteria and Assessment Office (ECAO). ECAO may be contacted at 513-569-7300 (FTS 684-7300) for general toxicological information as well as for technical guidance concerning route-to-route extrapolations, toxicity values for dermal exposures, and the evaluation of chemicals without toxicity values. The requestor should identify their need for a "rapid response request" (within 48 hours) for interim guidance on Superfund health-related issues. Contractors must give the name and address of their RPM or regional risk assessment contact before ECAO will respond. RPMs and regional contacts will be sent a copy of ECAO's response to the contractor.

Open literature. A primary literature search may be valuable for determining whether new data are available that may affect IRIS information.

7.4.2 DETERMINE TOXICITY VALUES FOR NONCARCINOGENIC EFFECTS (RfDs)

After general toxicity information for the chemicals of concern has been located, the next step is to identify the appropriate toxicity values to be used in evaluating noncarcinogenic effects associated with the specific exposures being assessed. First, by referring to the exposure information generated in Chapter 6, the exposure periods for which toxicity values are

necessary and the exposure route for each chemical being evaluated should be determined. The appropriate toxicity values for the chemical for each exposure duration and route of exposure can then be identified using the sources listed above.

For Superfund risk assessments, chronic RfDs should be identified for evaluating exposure periods between seven years and a lifetime, subchronic RfDs for exposure periods between two weeks and seven years, and One- or Ten-day Health Advisories for oral exposure periods of less than two weeks. According to EPA (1988c), One-day Health Advisories are applicable to exposure periods as long as two weeks. Developmental RfDs should be identified for evaluating single exposure events and other very short exposures (e.g., one day). Note that for some substances and some exposure situations, more than one of the toxicity values listed above may be needed to adequately assess potential noncarcinogenic effects.

Because carcinogens also commonly evoke noncarcinogenic effects, RfDs should be sought for all chemicals being carried through the risk assessment, including carcinogens. The RfDs derived for carcinogens, however, are based on noncancer effects and should not be assumed to be protective against carcinogenicity. A sample format for summarizing RfDs and other toxicity values is shown in Exhibit 7-2. This information will be needed in the risk characterization step (see Exhibits 8-3 and 8-4).

7.4.3 DETERMINE TOXICITY VALUES FOR CARCINOGENIC EFFECTS (SLOPE FACTORS)

In this step of the toxicity assessment, appropriate toxicity values for evaluating the carcinogenic risks associated with exposure are identified. First, by referring to the exposure information generated in Chapter 6, the route of exposure for the potential carcinogens being evaluated should be identified. Slope factors for these chemicals can then be identified using the hierarchy of sources listed in the box on page 7-15. Slope factors for all potential carcinogens having a weight-of-evidence classification of A, B, or C should be sought. A notation of the EPA weight-of-evidence classification should always be included with the slope factor. A sample format for summarizing the required toxicity values is shown in Exhibit 7-3. This information will be needed in the risk characterization step (see Exhibit 8-2).

7.5 EVALUATING CHEMICALS FOR WHICH NO TOXICITY VALUES ARE AVAILABLE

If EPA-derived RfDs and slope factors are available for the chemicals being examined, these values should always be used in the risk assessment. Use of EPA-derived toxicity values prevents duplication of effort and ensures consistency among risk assessments. If EPA-derived toxicity values are not available, the following measures are recommended.

7.5.1 ROUTE-TO-ROUTE EXTRAPOLATION

For cases in which EPA-derived toxicity values are not available for the route of exposure being considered but are available for another route, EPA recommends contacting ECAO for guidance on route-to-route extrapolation. If toxicity information is not available from ECAO, a qualitative rather than quantitative evaluation of the chemical is recommended. The implications of the absence of this chemical from the risk estimate should be discussed in the uncertainty section.

7.5.2 DERMAL EXPOSURE

No RfDs or slope factors are available for the dermal route of exposure. In some cases, however, noncarcinogenic or carcinogenic risks associated with dermal exposure can be evaluated using an oral RfD or oral slope factor, respectively. EPA recommends contacting ECAO for guidance on appropriate methods for evaluating dermal exposure for specific chemicals; some general guidance for calculating intakes via the dermal route and making appropriate comparisons with oral RfD values is given in Appendix A. In brief, exposures via the dermal route generally are calculated and expressed as absorbed doses. These absorbed doses are compared to an oral toxicity value that has been

adjusted, if necessary, so that it too is expressed as an absorbed dose.

It is inappropriate to use the oral slope factor to evaluate the risks associated with dermal exposure to carcinogens such as benz(a)pyrene, which cause skin cancer through a direct action at the point of application. These types of skin carcinogens and other locally active compounds must be evaluated separately from the above method; consult ECAO for guidance. Generally only a qualitative assessment of risks from dermal exposure to these chemicals is possible. This does not apply to carcinogens such as arsenic, which are believed to cause skin cancer through a systemic rather than local action.

If information is not available from ECAO, the assessor should describe the effects of the chemical qualitatively and discuss the implications of the absence of the chemical from the risk estimate in the uncertainty section of the risk assessment.

7.5.3 GENERATION OF TOXICITY VALUES

If EPA-derived toxicity values are unavailable but adequate toxicity studies are available, one may derive toxicity values using Agency methodology. Any such derivation should be done in conjunction with the regional risk assessment contact, who will submit the derivation to ECAO for approval. Contact with ECAO should be established early in the process to eliminate any duplication of effort because ECAO may have information on the chemical being evaluated.

7.6 UNCERTAINTIES RELATED TO TOXICITY INFORMATION

Toxicity information for many of the chemicals found at Superfund sites is often limited. Consequently, there are varying degrees of uncertainty associated with the toxicity values calculated. Sources of uncertainty associated with toxicity values may include:

- using dose-response information from effects observed at high doses to predict the adverse health effects that may occur following exposure to the low levels expected from human contact with the agent in the environment;

- using dose-response information from short-term exposure studies to predict the effects of long-term exposures, and vice-versa;

- using dose-response information from animal studies to predict effects in humans; and

- using dose-response information from homogeneous animal populations or healthy human populations to predict the effects likely to be observed in the general population consisting of individuals with a wide range of sensitivities.

An understanding of the degree of uncertainty associated with toxicity values is an important part of interpreting and using those values. Therefore, as part of the toxicity assessment for Superfund sites, a discussion of the strength of the evidence of the entire range of principal and supporting studies should be included. The degree of confidence ascribed to a toxicity value is a function of both the quality of the individual study from which it was derived and the completeness of the supporting data base. EPA-verified RfDs found in IRIS are accompanied by a statement of the confidence that the evaluators have in the RfD itself, the critical study, and the overall data base. All EPA-verified slope factors are accompanied by a weight-of-evidence classification, which indicates the likelihood that the agent is a human carcinogen. The weight-of-evidence classification is based on the completeness of the evidence that the agent causes cancer in experimental animals and humans. These designations should be used as one basis for the discussion of uncertainty.

EXHIBIT 7-2

EXAMPLE OF TABLE FORMAT FOR TOXICITY VALUES: POTENTIAL NONCARCINOGENIC EFFECTS

Chemical	Chronic RfD[a] (mg/kg-day)	Confidence Level[b]	Critical Effect	RfD Basis/ RfD Source	Uncertainty and Modifying Factors
Oral Route					
Phenol	0.6*	Medium	Kidney and liver effects	Water[c]/ IRIS	UF = 1,000[d] for H,A,S,L MF = 1
Nitrobenzene	0.0005*	Medium	Hematologic, adrenal, kidney, and liver effects	Water[c]/ IRIS	UF = 10,000 for H,A,S,L MF = 1
Inhalation Route					
—	—	—	—	—	—

* Values for illustration only.

[a] Similarly formatted tables also could be used for subchronic and shorter-term toxicity values.

[b] Confidence level from IRIS, either high, medium, or low.

[c] RfD expressed as administered dose in drinking water, with assumed absorption fraction of 1.0.

[d] Uncertainty adjustment of 1,000 used to represent combined H, A, S, and L extrapolations.

Uncertainty adjustments: H = variation in human sensitivity;
A = animal to human extrapolation;
S = extrapolation from subchronic to chronic NOAEL;
L = extrapolation from LOAEL to NOAEL.

EXHIBIT 7-3

EXAMPLE OF TABLE FORMAT FOR TOXICITY VALUES: POTENTIAL CARCINOGENIC EFFECTS

Chemical	Slope Factor (SF) $(mg/kg\text{-}day)^{-1}$	Weight-of-Evidence Classification	Type of Cancer[a]	SF Basis/ SF Source
Oral Route				
Benzene	0.029*	A*	Leukemia	Water[b]/ IRIS
Chlordane	1.3*	B2*	--	Water[b]/ IRIS
Inhalation Route				
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* Values for illustration only.

[a] Identity type(s) of cancer in this table for Class A carcinogens only.

[b] Slope factor based on administered dose in drinking water and assumed absorption fraction of 1.0.

The discussion of uncertainty also should include an indication of the extent to which an analysis of the results from different studies give a consistent, plausible picture of toxicity. The greater the strength of the evidence, the greater one's confidence in the conclusions drawn. The following factors add to the strength of the evidence that the chemical poses a hazard to humans and should be considered:

- similar effects across species, strains, sex, and routes of exposure;
- clear evidence of a dose-response relationship;
- a plausible relationship among data on metabolism, postulated mechanism of action, and the effect of concern (see Section 7.1.3);
- similar toxicity exhibited by structurally related compounds (see Section 7.1.3); and
- some link between the chemical and evidence of the effect of concern in humans (see Section 7.1.1).

High uncertainty (low confidence; low strength of evidence) indicates that the toxicity value might change if additional chronic toxicity data become available. Low uncertainty (high confidence) is an indication that a value is less likely to change as more data become available, because there is consistency among the toxic responses observed in different species, sexes, study designs, or in dose-response relationships. The lower the uncertainty about toxicity values, the more confidence a decision-maker can have in the risk assessment results. Often, high confidence is associated with values that are based on human data for the exposure route of concern.

7.7 SUMMARIZATION AND PRESENTATION OF THE TOXICITY INFORMATION

This section discusses methods for presenting toxicity information in the risk assessment document for the chemicals being evaluated.

7.7.1 TOXICITY INFORMATION FOR THE MAIN BODY OF THE TEXT

A short description of the toxic effects of each chemical carried through the assessment in non-technical language should be prepared for inclusion in the main body of the risk assessment. Included in this description should be information on the effects associated with exposure to the chemical and the concentrations at which the adverse effects are expected to occur in humans. Toxicity values should be accompanied by a brief description of the overall data base and the particular study from which the value was derived. In addition, a notation should be made of the critical effect and any uncertainty factors used in the calculation. For any RfD value obtained from IRIS, a notation of the degree of confidence associated with the determination should also be included. To aid in the risk characterization, it should be indicated if absorption efficiency was considered and also what exposure averaging periods are appropriate for comparison with the value.

Summary tables of toxicity values for all chemicals should be prepared for inclusion in the main body of the risk assessment report. RfDs in the table should be accompanied with the uncertainty factors used in their derivation, the confidence rating given in IRIS (if applicable), and a notation of the critical effect. Slope factors should always be accompanied by EPA's weight-of-evidence classification.

7.7.2 TOXICITY INFORMATION FOR INCLUSION IN AN APPENDIX

If toxicity values were derived in conjunction with the regional risk assessment contact and ECAO for chemicals lacking EPA-derived values, a technical documentation/justification of the method of derivation should be prepared and included in the appendix of the risk assessment report. Included in this explanation should be a description of the toxic effects of the chemical such as information regarding the noncarcinogenic, carcinogenic, mutagenic, reproductive, and developmental effects of the compound. Also presented should be brief

descriptions (species, route of administration, dosages, frequency of exposure, length of exposure, and critical effect) of the studies from which the values were derived as well as the actual method of derivation. References for the studies cited in the discussion should be included.

ENDNOTES FOR CHAPTER 7

1. The MF is set less than one for a small number of substances to account for nutritional essentiality.

2. The slope factor is occasionally referred to as a cancer potency factor; however, use of this terminology is not recommended.

3. The quantitative risk values and supporting information found in IRIS represent a consensus judgement of EPA's Reference Dose Workgroup or Carcinogen Risk Assessment Verification Endeavor (CRAVE) Workgroup. These workgroups are composed of scientists from EPA's program offices and the Office of Research and Development. The concept of Agency-wide consensus is one of the most valuable aspects of IRIS.

REFERENCES FOR CHAPTER 7

Environmental Protection Agency (EPA). 1986a. Guidelines for Carcinogen Risk Assessment. 51 Federal Register 33992 (September 24, 1986).

Environmental Protection Agency (EPA). 1986b. Guidelines for the Health Assessment of Suspect Developmental Toxicants. 51 Federal Register 34028 (September 24, 1986).

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Environmental Protection Agency (EPA). 1988b. Hazardous Substances Priority List, Toxicological Profiles; Second List. 53 Federal Register 41280 (October 20, 1988).

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Environmental Protection Agency (EPA). 1989f. Reference Dose (RfD): Description and Use in Health Risk Assessments. Appendix A to the Integrated Risk Information System (IRIS).

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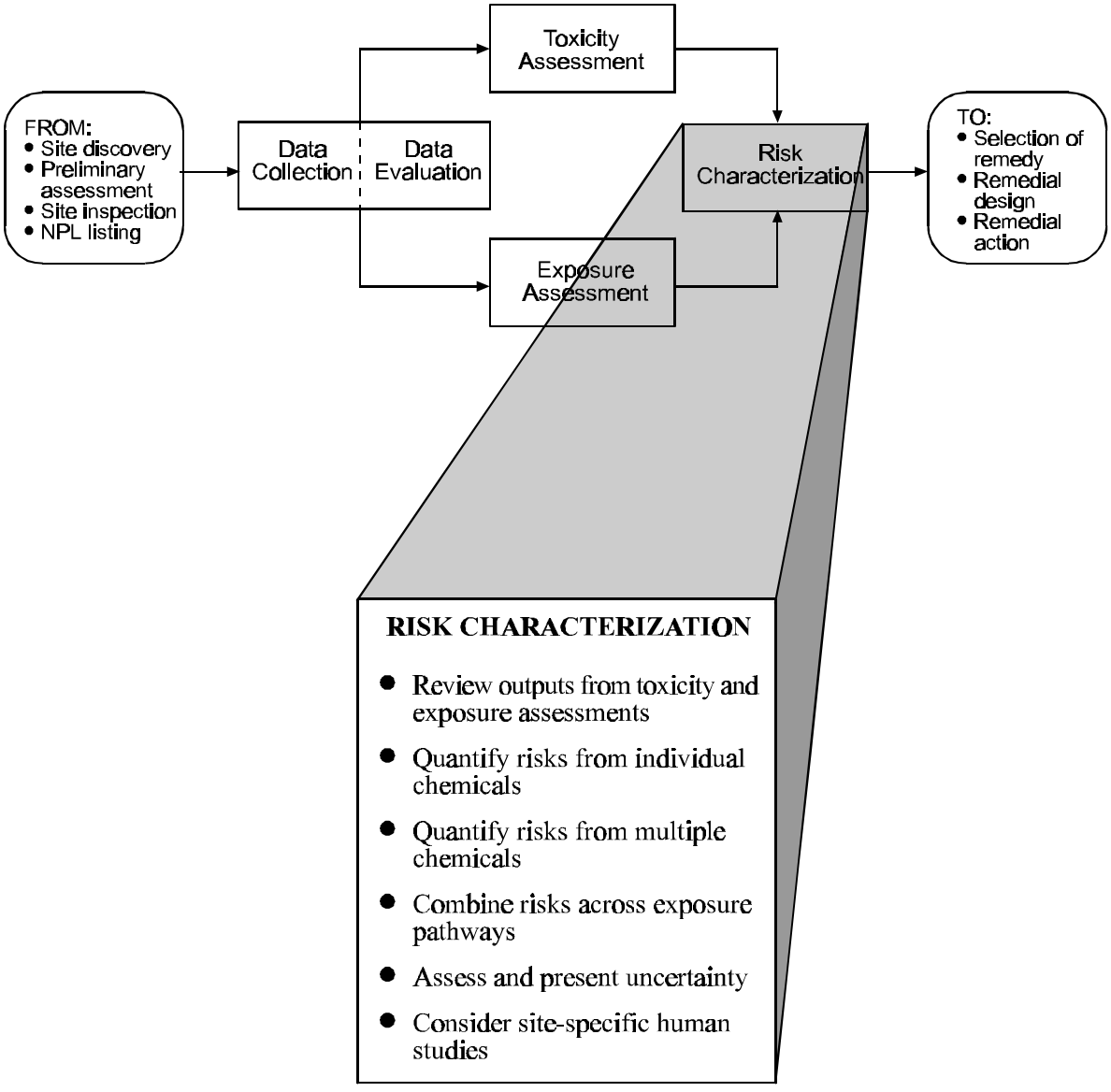
CHAPTER 8
RISK CHARACTERIZATION



CHAPTER 8

RISK CHARACTERIZATION

This chapter describes the final step of the baseline health risk assessment process, risk characterization. In this step, the toxicity and exposure assessments are summarized and integrated into quantitative and qualitative expressions of risk. To characterize potential noncarcinogenic effects, comparisons are made between projected intakes of substances and toxicity values; to characterize potential carcinogenic effects, probabilities that an individual will develop cancer over a lifetime of exposure are estimated from projected intakes and chemical-specific dose-response information. Major assumptions, scientific judgments, and to the extent possible, estimates of the uncertainties embodied in the assessment are also presented.

Risk characterization also serves as the bridge between risk assessment and risk management and is therefore a key step in the ultimate site decision-making process. This step assimilates risk assessment information for the risk manager (RPM or regional upper management involved in site decision-making) to be considered alongside other factors important for decision-making such as economics, technical feasibility, and regulatory context. The risk characterization methods described in this chapter are consistent with EPA's published risk assessment guidelines. Exhibit 8-1 is an overview of risk characterization, and illustrates how it relates to the preceding toxicity and exposure assessments and to the following development of preliminary remediation goals.

In the following sections, the risk characterization methodology is described. There are separate discussions for carcinogenic and noncarcinogenic effects because the methodology differs for these two modes of chemical toxicity. In addition to giving instructions for calculating numerical estimates of risk, this chapter provides guidance for interpreting, presenting, and qualifying the results. A risk characterization cannot be considered complete unless the numerical expressions of risk are accompanied by explanatory text interpreting and qualifying the results.

8.1 REVIEW OF OUTPUTS FROM THE TOXICITY AND EXPOSURE ASSESSMENTS

Most sites being assessed will involve the evaluation of more than one chemical of concern and might include both carcinogenic and noncarcinogenic substances. The first step in risk characterization is to gather, review, compare, and organize the results of the exposure assessment (e.g., intakes for all exposure pathways and land-uses and for all relevant substances) and toxicity assessment (e.g., toxicity values for all exposure

ACRONYMS FOR CHAPTER 8

ARAR = Applicable or Relevant and Appropriate Requirement
ATSDR= Agency for Toxic Substances and Disease Registry
CDI = Chronic Daily Intake
ECAO = Environmental Criteria and Assessment Office
E = Exposure Level
HI = Hazard Index
IRIS = Integrated Risk Information System
LOAEL = Lowest-Observed-Adverse-Effect-Level
NOAEL = No-Observed-Adverse-Effect-Level
NRC = Nuclear Regulatory Commission
RfD = Reference Dose (when used without other modifiers, RfD generally refers to chronic reference dose)
RfD_{dt} = Developmental Reference Dose
RfD_s = Subchronic Reference Dose
RI/FS = Remedial Investigation/Feasibility Study
RME = Reasonable Maximum Exposure
SDI = Subchronic Daily Intake
SF = Slope Factor

DEFINITIONS FOR CHAPTER 8

Absorbed Dose. The amount of a substance penetrating the exchange boundaries of an organism after contact. Absorbed dose is calculated from the intake and the absorption efficiency. It usually is expressed as mass of a substance absorbed into the body per unit body weight per unit time (e.g., mg/kg-day).

Administered Dose. The mass of substance given to an organism and in contact with an exchange boundary (e.g., gastrointestinal tract) per unit body weight per unit time (e.g., mg/kg-day).

Chronic Reference Dose (RfD). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. Chronic RfDs are specifically developed to be protective for long-term exposure to a compound (as a Superfund program guideline, seven years to lifetime).

Developmental Reference Dose (RfD_{dt}). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of an exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of development effects. Developmental RfDs are used to evaluate the effects of a single exposure event.

Exposure. Contact of an organism with a chemical or physical agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut) and available for absorption.

Exposure Assessment. The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure.

Exposure Pathway. The course a chemical or physical agent takes from a source to an exposed organism. An exposure pathway describes a unique mechanism by which an individual or population is exposed to chemicals or physical agents at or originating from a site. Each exposure pathway includes a source or release from a source, an exposure point, and an exposure route. If the exposure point differs from the source, a transport/exposure medium (e.g., air) or media (in cases of intermedia transfer) also is included.

Exposure Route. The way a chemical or physical agent comes in contact with an organism (e.g., by ingestion, inhalation, dermal contact).

Hazard Index (HI). The sum of more than one hazard quotient for multiple substances and/or multiple exposure pathways. The HI is calculated separately for chronic, subchronic, and shorter-duration exposures.

Hazard Quotient. The ratio of a single substance exposure level over a specified time period (e.g., subchronic) to a reference dose for that substance derived from a similar exposure period.

Intake. A measure of exposure expressed as the mass of a substance in contact with the exchange boundary per unit body weight per unit time (e.g., mg chemical/kg body weight-day). Also termed the normalized exposure rate; equivalent to administered dose.

Integrated Risk Information System (IRIS). An EPA data base containing verified RfDs and slope factors and up-to-date health risk and EPA regulatory information for numerous chemicals. IRIS is EPA's preferred source for toxicity information for Superfund.

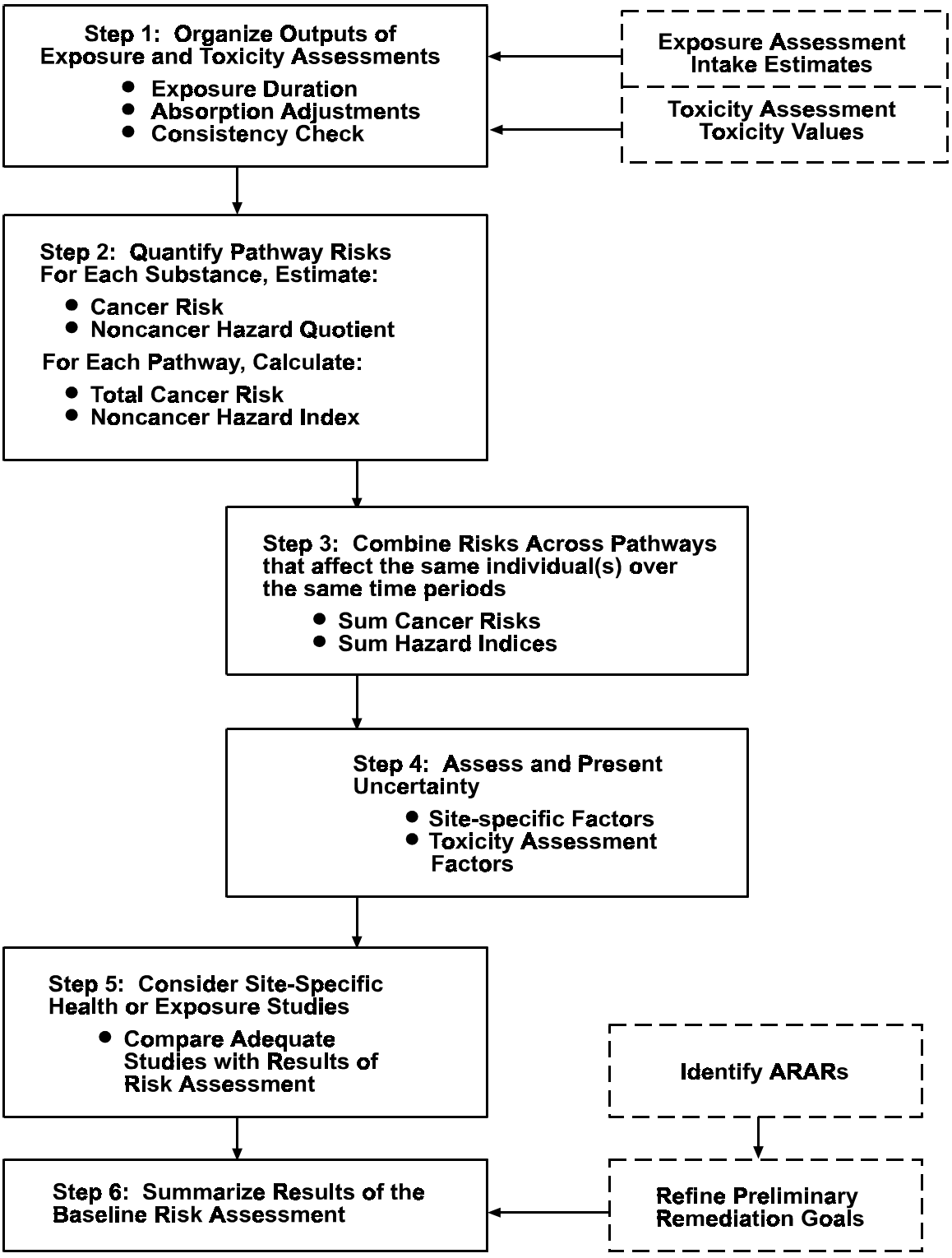
Reference Dose (RfD). The Agency's preferred toxicity value for evaluating noncarcinogenic effects result from exposures at Superfund sites. See specific entries for chronic RfD, subchronic RfD, and developmental RfD. The acronym RfD, when used without other modifiers, either refers generically to all types of RfDs or specifically to chronic RfDs; it never refers specifically to subchronic or developmental RfDs.

Slope Factor. A plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime. The slope factor is used to estimate an upper-bound probability of an individual developing cancer as a result of a lifetime of exposure to a particular level of a potential carcinogen.

Subchronic Reference Dose (RfD_s). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a portion of a lifetime (as a Superfund program guideline, two weeks to seven years).

Weight-of-Evidence Classification. An EPA classification system for characterizing the extent to which the available data indicate that an agent is a human carcinogen. Recently, EPA has developed weight-of-evidence classification systems for some other kinds of toxic effects, such as developmental effects.

EXHIBIT 8-1
STEPS IN RISK CHARACTERIZATION



routes and relevant substances). The following two subsections describe how to organize the outputs from the exposure and toxicity assessments and how to check for the consistency and validity of the information from the preceding exposure and toxicity assessments.

8.1.1 GATHER AND ORGANIZE INFORMATION

For each exposure pathway and land-use evaluated in the exposure assessment, check that all information needed to characterize risk is available. The necessary exposure information is outlined in the box below.

EXPOSURE INFORMATION NEEDED FOR RISK CHARACTERIZATION

- Estimated intakes (chronic, subchronic, and shorter-term, as appropriate) for chemicals.
- Important exposure modeling assumptions, including:
  - chemical concentration at the exposure points;
  - frequency and duration of exposure;
  - absorption assumptions; and
  - characterization of uncertainties.
- List of which exposure pathways can reasonably contribute to the exposure of the same individuals over the same time period.

For each chemical or substance evaluated in the toxicity assessment, use the checklist provided in the box below to ensure that all information needed to characterize risk is available.

8.1.2 MAKE FINAL CONSISTENCY AND VALIDITY CHECK

Check the consistency and validity of key assumptions common to the exposure outputs and the toxicity outputs for each contaminant and exposure pathway of concern. These assumptions include the averaging period for exposure, the exposure route, and the absorption adjustments. The basic principle is to ensure that the exposure estimates correspond as closely as possible with the assumptions used in developing the toxicity values.

TOXICITY INFORMATION NEEDED FOR RISK CHARACTERIZATION

- Slope factors for all carcinogenic chemicals.
- Discussion of weight of evidence and classifications for all carcinogenic chemicals.
- Type of cancer for Class A carcinogens.
- Chronic and subchronic RfDs and shorter-term toxicity values (if appropriate) for all chemicals (including carcinogens and developmental toxicants).
- Critical effect associated with each RfD.
- Discussion of uncertainties, uncertainty factors, and modifying factor used in deriving each RfD and "degree of confidence" in RfD (i.e., high, medium, low).
- Whether the toxicity values are expressed as absorbed or administered doses.
- Pharmacokinetic data that may affect the extrapolation from animals to humans for both the RfD and slope factor.
- Uncertainties in any route-to-route extrapolations.

Averaging period for exposure. If the toxicity value is based on average lifetime exposure (e.g., slope factors), then the exposure duration must also be expressed in those terms. For estimating cancer risks, always use average lifetime exposure; i.e., convert less-than-lifetime exposures to equivalent lifetime values (see EPA 1986a, *Guidelines for Carcinogen Risk Assessment)*. On the other hand, for evaluating potential noncarcinogenic effects of less-than-lifetime exposures, do not compare chronic RfDs to short-term exposure estimates, and do not convert short-term exposures to equivalent lifetime values to compare with the chronic RfDs. Instead, use subchronic or shorter-term toxicity values to evaluate short-term exposures. Check that the estimated exposure duration is sufficiently similar to the duration of the exposure in the study used to identify the toxicity value to be protective of human health (particularly for subchronic and shorter-term

effects). A toxicologist should review the comparisons. In the absence of short-term toxicity values, the chronic RfD may be used as an initial screening value; i.e., if the ratio of the short-term exposure value to the chronic RfD is less than one, concern for potential adverse health effects is low. If this ratio exceeds unity, however, more appropriate short-term toxicity values are needed to confirm the existence of a significant health threat. ECAO may be consulted for assistance in finding short-term toxicity values.

EPA ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE (ECAO) TECHNICAL ASSISTANCE

FTS 684-7300

513-569-7300

Exposure route. Check that all toxicity values used for each exposure pathway being evaluated at the site are consistent with the route of exposure (e.g., oral to oral, inhalation to inhalation). It is not possible to extrapolate between exposure routes for some substances that produce localized effects dependent upon the route of exposure. For example, a toxicity value based on localized lung tumors that result only from inhalation exposure to a substance would not be appropriate for estimating risks associated with dermal exposure to the substance. At this time, EPA considers it appropriate only to extrapolate dermal toxicity values from values derived for oral exposure. It is not recommended that oral toxicity reference values be extrapolated casually from inhalation toxicity values, although this extrapolation may be performed on a case-by-case basis in consultation with ECAO. In general, inhalation values should not be extrapolated from oral values. See Section 7.5.1 for additional information.

Inhalation RfD_i values obtained from IRIS will usually be expressed as ambient air concentrations (i.e., mg/m^3), instead of as administered doses (i.e., mg/kg-day). It may be necessary, therefore, to calculate the RfDi in units of mg/kg-day for comparison with the intake estimated in the exposure assessment. The RfD_i expressed in mg/kg-day would be equal to the RfD_i in mg/m^3 multiplied by 20 m^3 air inhaled per person per day divided by 70 kg per person.

Absorption adjustment. Check that the exposure estimates and the toxicity values are either both expressed as absorbed doses or both expressed as intakes (i.e., administered doses). Except for the dermal route of exposure, the exposure estimates developed using the methods provided in Chapter 6 should be in the form of intakes, with no adjustments made for absorption. However, there are three types of absorption adjustments that might be necessary or appropriate depending on the available toxicity information. These are described below. Sample calculations for these absorption adjustments are provided in Appendix A.

(1) Dermal exposures. The output of the exposure assessment for dermal exposure is expressed as the amount of substance absorbed per kg body weight per day. It therefore may be necessary to derive an absorbed-dose toxicity value from an administered-dose toxicity value to compare with the exposure estimate. See Appendix A for sample calculations.

(2) Absorbed-dose toxicity value. For the substances for which the toxicity value is expressed as an absorbed rather than administered dose (e.g., inhalation slope factor in IRIS for trichloroethylene and several other substances), one should express exposure as an absorbed dose rather than as an intake. See Appendix A.

(3) Adjustment for medium of exposure. Adjusting for different absorption efficiencies based on the medium of exposure (e.g., food, soil, or water for oral exposure, water or particulates for inhalation exposure) is occasionally appropriate, but not generally recommended unless there are strong arguments for doing so. Many oral RfD and slope factor values assume ingestion in water even when based on studies that employed administration in corn oil by gavage or in feed. Thus, in most cases, the unadjusted toxicity value will provide a

reasonable or conservative estimate of risk. See Appendix A.

8.2 QUANTIFYING RISKS

This section describes steps for quantifying risk or hazard indices for both carcinogenic and noncarcinogenic effects to be applied to each exposure pathway analyzed. The first subsection covers procedures for individual substances, and is followed by a subsection on procedures for quantifying risks associated with simultaneous exposures to several substances. Sample table formats for recording the results of these calculations as well as recording associated information related to uncertainty and absorption adjustments are provided in Exhibits 8-2 through 8-4.

8.2.1 CALCULATE RISKS FOR INDIVIDUAL SUBSTANCES

Carcinogenic effects. For carcinogens, risks are estimated as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to the potential carcinogen (i.e., incremental or excess individual lifetime cancer risk). The guidelines provided in this section are consistent with EPA's (1986a) *Guidelines for Carcinogen Risk Assessment*. For some carcinogens, there may be sufficient information on mechanism of action that a modification of the approach outlined below is warranted. Alternative approaches may be considered in consultation with ECAO on a case-by-case basis.

The slope factor (SF) converts estimated daily intakes averaged over a lifetime of exposure directly to incremental risk of an individual developing cancer. Because relatively low intakes (compared to those experienced by test animals) are most likely from environmental exposures at Superfund sites, it generally can be assumed that the dose-response relationship will be linear in the low-dose portion of the multistage model dose-response curve. (See the Background Document 2 of IRIS for a discussion of the multistage model). Under this assumption, the slope factor is a constant, and risk will be directly related to intake. Thus, the linear form of the carcinogenic risk equation is usually applicable for estimating Superfund site risks. This linear low-dose equation is described in the box below.

LINEAR LOW-DOSE CANCER RISK EQUATION

$$Risk = CDI \times SF$$

where:

Risk	=	a unitless probability (e.g., 2×10^{-5}) of an individual developing cancer;
CDI	=	chronic daily intake averaged over 70 years (mg/kg-day); and
SF	=	slope factor, expressed in $(mg/kg\text{-}day)^{-1}$.

The CDI is identified in Exhibits 6-11 through 6-19 and 6-22 and the SF is identified in Exhibit 7-3.

However, this linear equation is valid only at low risk levels (i.e., below estimated risks of 0.01). For sites where chemical intakes might be high (i.e., risk above 0.01), an alternate calculation equation should be used. The one-hit equation, which is consistent with the linear low-dose model given above and described in the box on page 8-11, should be used instead.

Because the slope factor is often an upper 95th percentile confidence limit of the probability of response based on experimental animal data used in the multistage model, the carcinogenic risk estimate will generally be an upper-bound estimate. This means that EPA is reasonably confident that the "true risk" will not exceed the risk estimate derived through use of this model and is likely to be less than that predicted.

Noncarcinogenic effects. The measure used to describe the potential for noncarcinogenic toxicity to occur in an individual is not expressed as the probability of an individual suffering an adverse effect. EPA does not at the present time use a probabilistic approach to estimating the potential for noncarcinogenic health effects. Instead, the

EXHIBIT 8-2

EXAMPLE OF TABLE FORMAT FOR CANCER RISK ESTIMATES

Chemical	CDI (mg/kg-day)	CDI Adj. for Absorp.	SF $(mg/kg\text{-}day)^{-1}$	Weight of Evidence	Type of Cancer[a]	SF Source	SF Basis (Vehicle)	Chemical-specific Risk[b]	Total Pathway Risk[b]	Total Exposure Risk[b]
Exposure Pathway: Ingestion of Contaminated Private Well Water										
Benzene	0.00025*	No	0.029*	A*	Leukemia	HEA	Water[c]	$7x10^{-6}$		
Chlordane	0.00015*	No	1.3*	B2*		IRIS	Water[c]	$2x10^{-4}$	$2x10^{-4}$	
Exposure Pathway: Ingestion of Contaminated Fish										
Chlordane	0.00008*	No	1.3*	B2*		IRIS	Water[c]	$1x10^{-4}$	$1x10^{-4}$	
Nearby Residential Population in Area Y – Total Cancer Risk (weight of evidence predominantly B2)[d]										$3x10^{-4}$

* Values for illustration only.
[a] Identify type of cancer in this table for Class A carcinogens only.
[b] All cancer risks should be expressed as one significant figure only.
[c] Slope factor based on dose administered in drinking water and assumed absorption fraction of 1.0.
[d] Summarize weight of evidence for carcinogens contributing most to the total cancer risk estimate.

SF = Slope Factor
CDI = Chronic Daily Intake

EXHIBIT 8-3

EXAMPLE OF TABLE FORMAT FOR CHRONIC HAZARD INDEX ESTIMATES

Chemical	CDI (mg/kg-day)	CDI Adjusted for Absorption	RfD (mg/kg-day)	Confidence Level	Critical Effect	RfD Source	RfD Basis (Vehicle)	RfD Uncertainty Adjustments	Modifying Factor	Hazard Quotient[a]	Pathway Hazard Index[a]	Total Exposure Hazard Index[a]
Exposure Pathway: Ingestion of Contaminated Private Well Water												
Phenol	0.1*	No	0.6*	M	Kidney, liver	IRIS	Water[c]	H,A,S,L*[d]	1*	0.2		
Nitrobenzene	0.0001*	No	0.0005*	M	Several	IRIS	Water[c]	H,A,S,L*	1*	0.2		
Cyanide	0.0003*	No	0.02*	M	Thyroid	IRIS	Water[c]	H,A*	5*	0.02	0.4[b]	
Exposure Pathway: Ingestion of Contaminated Fish												
Phenol	0.08*	Yes	0.6*	M	Kidney, liver	IRIS	Water[c]	H,A,S,L*[d]	1*	0.1		
MEK	0.005*	Yes	0.05*	M	CNS fetotox	IRIS	Water[c]	H,A,S*	1*	0.1	0.2[b]	
Nearby Residential Population in Area Y – Total Chronic Hazard Index												0.6[b]

* Values for illustration only.

[a] All hazard indices and hazard quotients should be expressed as one significant figure only.

[b] If the hazard index is greater than 1.0, see Section 8.2.2 for guidance on possible segregation of hazard index by endpoint.

[c] RfD expressed as administered dose.

[d] Uncertainty adjustment of 1,000 used to represent combined H, A, S, & L extrapolations.

Abbreviation for Uncertainty Adjustments: Factor of 10 used for each adjustment, unless indicated otherwise.

H = variation in human sensitivity
A = animal to human extrapolation
S = extrapolation from subchronic to chronic NOAEL
L = extrapolation from LOAEL to NOAEL

MF = Modifying factor for EPA verified RfDs. This factor represents professional judgement on overall data base not specifically addressed by uncertainty adjustments.

CDI = Chronic Daily Intake
RfD = Chronic Reference Dose

Confidence Level: L = low, M = medium, H = high.

EXHIBIT 8-4

EXAMPLE OF TABLE FORMAT FOR SUBCHRONIC HAZARD INDEX ESTIMATES

Chemical	SDI (mg/kg-day)	SDI Adjusted for Absorption	RfD_s (mg/kg-day)	Critical Effect	RfD_s Source	RfD_s Basis (Vehicle)	RfD_s Uncertainty Adjustments	Modifying Factor	Hazard Quotient[a]	Pathway Hazard Index[a]	Total Exposure Hazard Index[a]
Exposure Pathway: Ingestion of Contaminated Schoolyard Soil/Six Years											
Manganese	0.02*	Yes	0.5*	CNS, repro.	HEA	Water[c]	H, A*	1*	0.04		
Selenium	0.0008*	Yes	0.004*	Several	HEA	Water[c]	H, A*	1.5*	0.2		
Mercury	0.00001*	Yes	0.0003*	CNS	HEA	Water[c]	H*	1*	0.03		
Tin	0.006*	No	0.6*	Liver, kidney	HEA	Food[c]	H, A*	1*	0.01		0.3[b]
Nearby Elementary Schoolyard – Total Subchronic Hazard Index											0.3[b]

* Values for illustration only.

[a] All hazard indices and hazard quotients should be expressed as one significant figure only.

[b] If hazard index is greater than 1.0, see Section 8.2.2 for guidance on possible segregation of hazard index by endpoint.

[c] RfDs expressed as administered dose.

Abbreviation for Uncertainty Adjustments: Factor of 10 used for each adjustment, unless indicated otherwise.

H = variation in human sensitivity
A = animal to human extrapolation
L = extrapolation from LOAEL to NOAEL

MF = Modifying factor for EPA RfD_ss. This factor represents professional judgement on overall data base not specifically addressed by uncertainty adjustments.

SDI = Subchronic Daily Intake
RfD_s = Subchronic Reference Dose

EXPLANATION OF SAMPLE TABLE FORMAT FOR CANCER RISK ESTIMATES

A sample table format for summarizing cancer risk estimates is provided in Exhibit 8-2. For each baseline risk assessment, at least two summary tables generally would be required: one for current land uses and one for future land uses. In the example provided in Exhibit 8-2, two exposure pathways were determined to contribute to exposure of a nearby residential population under current land use: ingestion of private well water contaminated with benzene and chlordane and ingestion of fish contaminated with chlordane. Moreover, a subset of the population in Area Y was exposed to the maximal well water contamination and consumed more locally caught fish than the remainder of the nearby population.

Values for the chronic daily intake (CDI), averaged over a lifetime, of each contaminant by each exposure pathway would be obtained from a table such as that shown in Exhibit 6-22. The CDI via well water was not adjusted for absorption efficiency because the slope factors for these substances assume ingestion in water and an absorption fraction of 1.0. The CDI for chlordane in fish was not adjusted for vehicle of exposure (i.e., food versus water) because absorption efficiency data were limited, and an absorption fraction of 1.0 was used as a conservative assumption. If, for example, available data had indicated that only 10 percent of chlordane ingested with fish is absorbed, the CDI could have been adjusted downward to 0.000008 mg/kg-day (i.e., 0.00008 mg/kg-day x 0.10 absorption fraction).

Values for the slope factors (SF), weight-of-evidence classification, type of cancer (for Class A carcinogens), reference source of the SF, and basis of the SF (vehicle of administration and absorption efficiency) would be obtained from a table such as that shown in Exhibit 7-3. The chemical-specific risks were calculated from the CDI and SF using the linear low-dose cancer risk equation (risk = CDI x SF). The total pathway risk for ingestion of private well water is the sum of the two chemical-specific risks for that pathway. The total risk estimate for the nearby residential population in area Y is the sum of the cancer risks for the two pathways. Note that it is important to summarize the weight of evidence for the carcinogens contributing most to the total cancer risk estimate; in this example, chlordane, a Class B2 carcinogen, accounted for most of the risk.

EXPLANATION OF SAMPLE TABLE FORMAT FOR CHRONIC HAZARD INDEX ESTIMATES

A sample table format for summarizing chronic hazard index estimates is provided in Exhibit 8-3. For each baseline risk assessment, at least two summary tables generally would be required: one for current land uses and one for future land uses. In the example provided in Exhibit 8-3, two exposure pathways were determined to contribute to exposure of a nearby residential population under current land use: ingestion of private well water contaminated with phenol, nitrobenzene, and cyanide and ingestion of fish contaminated with phenol and methyl ethyl ketone (MEK). Moreover, a subset of the population in Area Y was exposed to the maximal well water contamination and consumed more locally caught fish than the remainder of the nearby population.

Values for the chronic daily intake (CDI), averaged over the period of exposure, of each contaminant by each exposure pathway would be obtained from a table such as that shown in Exhibit 6-22. The CDI via well water was not adjusted for absorption efficiency because the RfDs for these substances are based on ingestion in water and an absorption fraction of 1.0. The CDI for phenol and MEK in fish was not adjusted for vehicle of exposure (i.e., food versus water) because absorption efficiency data were limited, and an absorption fraction of 1.0 was used as a conservative assumption. If, for example, available data had indicated that only 20 percent of MEK ingested with fish is absorbed, the CDI for MEK could have been adjusted downward to 0.001 mg/kg-day (i.e., 0.005 mg/kg-day x 0.20 absorption efficiency).

Values for the RfDs, confidence level in the RfD, critical effect, source of the value, and basis of the RfD (vehicle of administration and absorption efficiency) would be obtained from a table such as that shown in Exhibit 7-2. The chemical-specific hazard quotients are equal to the CDI divided by the RfD. The total pathway hazard index for ingestion of private well water is the sum of the three chemical-specific hazard quotients for that pathway. The total hazard index estimate for the nearby residential population in area Y is the sum of the hazard indices for the two exposure pathways.

Note that it is important to include the noncarcinogenic effects of carcinogenic substances when appropriate reference doses are available. For example, in an actual risk assessment of the chemicals summarized in Exhibit 6-22, the potential noncarcinogenic effects of chlordane should be evaluated and appropriate entries made in tables such as those shown in Exhibits 7-2 and 8-3.

ONE-HIT EQUATION FOR HIGH CARCINOGENIC RISK LEVELS

$$Risk = 1 - \exp(-CDI \times SF)$$

where:

Risk = a unitless probability (e.g., 2 x 10^{-5}) of an individual developing cancer;

exp = the exponential;

CDI = chronic daily intake averaged over 70 years (mg/kg-day); and

NONCANCER HAZARD QUOTIENT

Noncancer Hazard Quotient = E/RfD

where:

E = exposure level (or intake);

RfD = reference dose; and

E and RfD are expressed in the same

potential for noncarcinogenic effects is evaluated by comparing an exposure level over a specified time period (e.g., lifetime) with a reference dose derived for a similar exposure period. This ratio of exposure to toxicity is called a hazard quotient and is described in the box in the opposite column.

The noncancer hazard quotient assumes that there is a level of exposure (i.e., RfD) below which it is unlikely for even sensitive populations to experience adverse health effects. If the exposure level (E) exceeds this threshold (i.e., if E/RfD exceeds unity), there may be concern for potential noncancer effects. As a rule, the greater the value of E/RfD above unity, the greater the level of concern. Be sure, however, not to interpret ratios of E/RfD as statistical probabilities; a ratio of 0.001 does not mean that there is a one in one thousand chance of the effect occurring. Further, it is important to emphasize that the level of concern does not increase linearly as the RfD is approached or exceeded because RfDs do not have equal accuracy or precision and are not based on the same severity of toxic effects. Thus, the slopes of the dose-response curve in excess of the RfD can range widely depending on the substance.

Three exposure durations that will need separate consideration for the possibility of adverse noncarcinogenic health effects are chronic, subchronic, and shorter-term exposures. As guidance for Superfund, chronic exposures for humans range in duration from seven years to a lifetime; such long-term exposures are almost always of concern for Superfund sites (e.g., inhabitants of nearby residences, year-round users of specified drinking water sources). Subchronic human exposures typically range in duration from two weeks to seven years and are often of concern at Superfund sites. For example, children might attend a junior high school near the site for no more than two or three years. Exposures less than two weeks in duration are occasionally of concern at Superfund sites. For example, if chemicals known to be developmental toxicants are present at a site, short-term exposures of only a day or two can be of concern.

8.2.2 AGGREGATE RISKS FOR MULTIPLE SUBSTANCES

At most Superfund sites, one must assess potential health effects of more than one chemical (both carcinogens and other toxicants). Estimating risk or hazard potential by considering one chemical at a time might significantly underestimate the risks associated with simultaneous exposures to several substances. To assess the overall potential for cancer and noncancer effects posed by multiple chemicals, EPA (1986b) has developed *Guidelines for the Health Risk Assessment of Chemical Mixtures* that can also be applied to the case of simultaneous exposures to several chemicals from a variety of sources by more than one exposure pathway. Although the calculation procedures differ for

carcinogenic and noncarcinogenic effects, both sets of procedures assume dose additivity in the absence of information on specific mixtures.

Information on specific mixtures found at Superfund sites is rarely available. Even if such data exist, they are often difficult to use. Monitoring for "mixtures" or modeling the movement of mixtures across space and time present technical problems given the likelihood that individual components will behave differently in the environment (i.e., fate and transport). If data are available on the mixtures present at the site, but are not adequate to support a quantitative evaluation, note the information in the "assumptions" documentation.

Carcinogenic effects. The cancer risk equation described in the box below estimates the incremental individual lifetime cancer risk for simultaneous exposure to several carcinogens and is based on EPA's (1986a,b) risk assessment guidelines. This equation represents an approximation of the precise equation for combining risks which accounts for the joint probabilities of the same individual developing cancer as a consequence of exposure to two or more carcinogens.[1] The difference between the precise equation and the approximation described in the box is negligible for total cancer risks less than 0.1. Thus, the simple additive equation is appropriate for most Superfund risk assessments.

CANCER RISK EQUATION FOR MULTIPLE SUBSTANCES

$$Risk_T = \Sigma\ Risk_i$$

where:

$Risk_T$ = the total cancer risk, expressed as a unitless probability; and

$Risk_i$ = the risk estimate for the i^{th} substance.

The risk summation techniques described in the box on this page and in the footnote assume that intakes of individual substances are small. They also assume independence of action by the compounds involved (i.e., that there are no synergistic or antagonistic chemical interactions and that all chemicals produce the same effect, i.e., cancer). If these assumptions are incorrect, over- or under-estimation of the actual multiple-substance risk could result.

Calculate a separate total cancer risk for each exposure pathway by summing the substance-specific cancer risks. Resulting cancer risk estimates should be expressed using one significant figure only. Obviously, the total cancer risk for each pathway should not exceed 1. Exhibit 8-2 provides a sample table format for presenting estimated cancer risks for specified exposure pathways in the "Total Pathway Risk" column.

There are several limitations to this approach that must be acknowledged. First, because each slope factor is an upper 95th percentile estimate of potency, and because upper 95th percentiles of probability distributions are not strictly additive, the total cancer risk estimate might become artificially more conservative as risks from a number of different carcinogens are summed. If one or two carcinogens drive the risk, however, this problem is not of concern. Second, it often will be the case that substances with different weights of evidence for human carcinogenicity are included. The cancer risk equation for multiple substances sums all carcinogens equally, giving as much weight to class B or C as to class A carcinogens. In addition, slope factors derived from animal data will be given the same weight as slope factors derived from human data. Finally, the action of two different carcinogens might not be independent. New tools for assessing carcinogen interactions are becoming available, and should be considered in consultation with the RPM (e.g., Arcos *et al*. 1988). The significance of these concerns given the circumstances at a particular site should be discussed and presented with the other information described in Section 8.6.

Noncarcinogenic effects. To assess the overall potential for noncarcinogenic effects posed by more than one chemical, a hazard index (HI) approach has been developed based on EPA's (1986b) *Guidelines*

for Health Risk Assessment of Chemical Mixtures. This approach assumes that simultaneous subthreshold exposures to several chemicals could result in an adverse health effect. It also assumes that the magnitude of the adverse effect will be proportional to the sum of the ratios of the subthreshold exposures to acceptable exposures. The hazard index is equal to the sum of the hazard quotients, as described in the box below, where E and the RfD represent the same exposure period (e.g., subchronic, chronic, or shorter-term). When the hazard index exceeds unity, there may be concern for potential health effects. While any single chemical with an exposure level greater than the toxicity value will cause the hazard index to exceed unity, for multiple chemical exposures, the hazard index can also exceed unity even if no single chemical exposure exceeds its RfD.

NONCANCER HAZARD INDEX

$$\text{Hazard Index} = E_1/RfD_1 + E_2/RfD_2 + ... + E_i/RfD_i$$

where:

E_i = exposure level (or intake) for the i^{th} toxicant;

RfD_i = reference dose for the i^{th} toxicant; and

E and RfD are expressed in the same units and represent the same exposure period (i.e., chronic, subchronic, or shorter-term).

It is important to calculate the hazard index separately for chronic, subchronic, and shorter-term exposure periods as described below. It is also important to remember to include RfDs for the noncancer effects of carcinogenic substances.

(1) Noncarcinogenic effects -- chronic exposures. For each chronic exposure pathway (i.e., seven year to lifetime exposure), calculate a separate chronic hazard index from the ratios of the chronic daily intake (CDI) to the chronic reference dose (RfD) for individual chemicals as described in the box below. Exhibit 8-3 provides a sample table format for recording these results in the "Pathway Hazard Index" column.

CHRONIC NONCANCER HAZARD INDEX

$$\text{Chronic Hazard Index} = CDI_1/RfD_1 + CDI_2/RfD_2 + ... + CDI_i/RfD_i$$

where:

CDI_i = chronic daily intake for the i^{th} toxicant in mg/kg-day, and

RfD_i = chronic reference dose for the i^{th} toxicant in mg/kg-day.

The CDI is identified in Exhibits 6-11 through 6-19 and 6-22 and the RfD is identified in Exhibit 7-2.

(2) Noncarcinogenic effects -- subchronic exposures. For each subchronic exposure pathway (i.e., two week to seven year exposure), calculate a separate subchronic hazard index from the ratios of subchronic daily intake (SDI) to the subchronic reference dose (RfD_s) for individual chemicals as described in the box on the next page. Exhibit 8-4 provides a sample table format for recording these results in the "Pathway Hazard Index" column. Add only those ratios corresponding to subchronic exposures that will be occurring simultaneously.

(3) Noncarcinogenic effects -- less than two week exposures. The same procedure may be applied for simultaneous shorter-term exposures to several chemicals. For drinking water exposures, 1- and 10-day Health Advisories can be used as reference toxicity values. Depending on available data, a separate hazard index might also be calculated for developmental toxicants (using RfD_{dt}s), which might cause adverse effects following exposures of only a few days. See

SUBCHRONIC NONCANCER HAZARD INDEX

Subchronic
Hazard Index $= SDI_1/RfD_{s1}+SDI_2/RfD_{s2} + ... + SDI_i/RfD_{si}$

where:

SDI_i = subchronic daily intake for the i^{th} toxicant in mg/kg-day; and

RfD_{si} = subchronic reference dose for the i^{th} toxicant in mg/kg-day.

Guidelines for the Health Assessment of Suspect Developmental Toxicants (EPA 1986c; EPA 1989) for further guidance.

There are several limitations to this approach that must be acknowledged. As mentioned earlier, the level of concern does not increase linearly as the reference dose is approached or exceeded because the RfDs do not have equal accuracy or precision and are not based on the same severity of effect. Moreover, hazard quotients are combined for substances with RfDs based on critical effects of varying toxicological significance. Also, it will often be the case that RfDs of varying levels of confidence that include different uncertainty adjustments and modifying factors will be combined (e.g., extrapolation from animals to humans, from LOAELs to NOAELs, from one exposure duration to another).

Another limitation with the hazard index approach is that the assumption of dose additivity is most properly applied to compounds that induce the same effect by the same mechanism of action. Consequently, application of the hazard index equation to a number of compounds that are not expected to induce the same type of effects or that do not act by the same mechanism could overestimate the potential for effects, although such an approach is appropriate at a screening level. This possibility is generally not of concern if only one or two substances are responsible for driving the HI above unity. If the HI is greater than unity as a consequence of summing several hazard quotients of similar value, it would be appropriate to segregate the compounds by effect and by mechanism of action and to derive separate hazard indices for each group.

Segregation of hazard indices. Segregation of hazard indices by effect and mechanism of action can be complex and time-consuming because it is necessary to identify all of the major effects and target organs for each chemical and then to classify the chemicals according to target organ(s) or mechanism of action. This analysis is not simple and should be performed by a toxicologist. If the segregation is not carefully done, an underestimate of true hazard could result. Agency review of particularly complex or controversial cases can be requested of ECAO through the regional risk assessment support staff.

The procedure for recalculating the hazard index by effect and by mechanism of action is briefly described in the box on the next page. If one of the effect-specific hazard indices exceeds unity, consideration of the mechanism of action might be warranted. A strong case is required, however, to indicate that two compounds which produce adverse effects on the same organ system (e.g., liver), although by different mechanisms, should not be treated as dose additive. Any such determination should be reviewed by ECAO.

If there are specific data germane to the assumption of dose-additivity (e.g., if two compounds are present at the same site and it is known that the combination is five times more toxic than the sum of toxicities for the two compounds), then modify the development of the hazard index accordingly. Refer to the EPA (1986b) mixtures guidelines for discussion of a hazard index equation that incorporates quantitative interaction data. If data on chemical interactions are available, but are not adequate to support a quantitative assessment, note the information in the "assumptions" being documented for the site risk assessment.

PROCEDURE FOR SEGREGATION OF HAZARD INDICES BY EFFECT

Segregation of hazard indices requires identification of the major effects of each chemical, including those seen at higher doses than the critical effect (e.g., the chemical may cause liver damage at a dose of 100 mg/kg-day and neurotoxicity at a dose of 250 mg/kg-day). Major effect categories include neurotoxicity, developmental toxicity, reproductive toxicity, immunotoxicity, and adverse effects by target organ (i.e., hepatic, renal, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, and dermal/ocular effects). Although higher exposure levels may be required to produce adverse health effects other than the critical effect, the RfD can be used as the toxicity value for each effect category as a conservative and simplifying step.

INFORMATION SOURCES FOR SEGREGATION OF HAZARD INDICES

Of the available information sources, the ATSDR Toxicological Profiles are well suited in format and content to allow a rapid determination of additional health effects that may occur at exposure levels higher than those that produce the critical effect. Readers should be aware that the ATSDR definitions of exposure durations are somewhat different than EPA's and are independent of species; acute -- up to 14 days; intermediate -- more than 14 days to 1 year; chronic -- greater than one year. IRIS contains only limited information on health effects beyond the critical effect, and EPA criteria documents and HEAs, HEEPs, and HEEDs may not systematically cover all health effects observed at doses higher those associated with the most sensitive effects.

8.3 COMBINING RISKS ACROSS EXPOSURE PATHWAYS

This section gives directions for combining the multi-chemical risk estimates across exposure pathways and provides guidance for determining when such aggregation is appropriate.

In some Superfund site situations, an individual might be exposed to a substance or combination of substances through several pathways. For example, a single individual might be exposed to substance(s) from a hazardous waste site by consuming contaminated drinking water from a well, eating contaminated fish caught near the site, and through inhalation of dust originating from the site. The total exposure to various chemicals will equal the sum of the exposures by all pathways. One should not automatically sum risks from all exposure pathways evaluated for a site, however. The following subsections describe how to identify exposure pathways that should be combined and, for these, how to sum cancer risks and noncancer hazard indices across multiple exposure pathways.

8.3.1 IDENTIFY REASONABLE EXPOSURE PATHWAY COMBINATIONS

There are two steps required to determine whether risks or hazard indices for two or more pathways should be combined for a single exposed individual or group of individuals . The first is to identify reasonable exposure pathway combinations. The second is to examine whether it is likely that the same individuals would consistently face the "reasonable maximum exposure" (RME) by more than one pathway.

Identify exposure pathways that have the potential to expose the same individual or subpopulation at the key exposure areas evaluated in the exposure assessment, making sure to consider areas of highest exposure for each pathway for both current and future land-uses (e.g., nearest downgradient well, nearest downwind receptor). For each pathway, the risk estimates and hazard indices have been developed for a particular exposure area and time period; they do not necessarily apply to other locations or time periods. Hence, if two pathways do not affect the same individual or subpopulation, neither pathway's individual risk estimate or hazard index affects the other, and risks should not be combined.

Once reasonable exposure pathway combinations have been identified, it is necessary to examine whether it is likely that the same individuals would consistently face the RME as estimated by the methods described in Chapter 6. Remember that the RME estimate for each exposure pathway includes many conservative and upper-bound parameter values and assumptions (e.g., upper 95th confidence limit on amount of water ingested, upper-bound duration of occupancy of a single residence). Also,

some of the exposure parameters are not predictable in either space or time (e.g., maximum downwind concentration may shift compass direction, maximum ground-water plume concentration may move past a well). For real world situations in which contaminant concentrations vary over time and space, the same individual may or may not experience the RME for more than one pathway over the same period of time. One individual might face the RME through one pathway, and a different individual face the RME through a different pathway. Only if you can explain why the key RME assumptions for more than one pathway apply to the same individual or subpopulation should the RME risks for more than one pathway be combined.

In some situations, it may be appropriate to combine one pathway's RME risks with other pathways' risk estimates that have been derived from more typical exposure parameter values. In this way, resulting estimates of combined pathway risks may better relate to RME conditions.

If it is deemed appropriate to sum risks and hazard indices across pathways, the risk assessor should clearly identify those exposure pathway combinations for which a total risk estimate or hazard index is being developed. The rationale supporting such combinations should also be clearly stated. Then, using the methods described in Sections 8.3.2 and 8.3.3, total cancer risk estimates and hazard indices should be developed for the relevant exposure areas and individuals (or subpopulations). For example, Exhibits 8-2 and 8-3 illustrate the combination of cancer risk estimates and chronic noncancer hazard indices, respectively, for a hypothetical nearby residential population exposed to contaminants from a site by two exposure pathways: drinking contaminated ground water from private wells and ingestion of contaminated fish caught in the local river. In this hypothetical example, it is "known" that the few families living next to the site consume more locally caught fish than the remaining community and have the most highly contaminated wells of the area.

The following two subsections describe how to sum risks and hazard indices for multiple exposure pathways for carcinogenic and noncarcinogenic substances, respectively.

8.3.2 SUM CANCER RISKS

First, sum the cancer risks for each exposure pathway contributing to exposure of the same individual or subpopulation. For Superfund risk assessments, cancer risks from various exposure pathways are assumed to be additive, as long as the risks are for the same individuals and time period (i.e., less-than-lifetime exposures have all been converted to equivalent lifetime exposures). This summation is described in the box below. The sample table format given in Exhibit 8-2 provides a place to record the total cancer risk estimate.

CANCER RISK EQUATION FOR MULTIPLE PATHWAYS

Total Exposure Cancer Risk =

$Risk(\text{exposure pathway}_1) +$
$Risk(\text{exposure pathway}_2) + \ldots\ldots +$
$Risk(\text{exposure pathway}_i)$

As described in Section 8.2.2, although the exact equation for combining risk probabilities includes terms for joint risks, the difference between the exact equation and the approximation described above is negligible for total cancer risks of less than 0.1.

8.3.3 SUM NONCANCER HAZARD INDICES

To assess the overall potential for noncarcinogenic effects posed by several exposure pathways, the total hazard index for each exposure duration (i.e., chronic, subchronic, and shorter-term) should be calculated separately. This equation is described in the box on the next page. The sample table format given in Exhibit 8-3 provides a place to record the total exposure hazard index for chronic exposure durations.

When the total hazard index for an exposed individual or group of individuals exceeds unity, there may be concern for potential noncancer health effects. For multiple exposure pathways, the hazard index can exceed unity even if no single exposure pathway hazard index exceeds unity. If the total hazard index exceeds unity and if combining exposure pathways has resulted in combining hazard indices based on different chemicals, one may need

HAZARD INDEX EQUATION FOR MULTIPLE PATHWAYS

Total Exposure Hazard Index =

Hazard Index(exposure pathway$_1$) +
Hazard Index(exposure pathway$_2$) + ... +
Hazard Index(exposure pathway$_i$)

where:

Total Exposure Hazard Index is calculated separately for chronic, subchronic, and shorter-term exposure periods.

to consider segregating the contributions of the different chemicals according to major effect (see Section 8.2.2.).

8.4 ASSESSMENT AND PRESENTATION OF UNCERTAINTY

This section discusses practical approaches to assessing uncertainty in Superfund site risk assessments and describes ways to present key information bearing on the level of confidence in quantitative risk estimates for a site. The risk measures used in Superfund site risk assessments usually are not fully probabilistic estimates of risk, but conditional estimates given a considerable number of assumptions about exposure and toxicity (e.g., risk given a particular future land-use). Thus, it is important to fully specify the assumptions and uncertainties inherent in the risk assessment to place the risk estimates in proper perspective. Another use of uncertainty characterization can be to identify areas where a moderate amount of additional data collection might significantly improve the basis for selection of a remedial alternative.

Highly quantitative statistical uncertainty analysis is usually not practical or necessary for Superfund site risk assessments for a number of reasons, not the least of which are the resource requirements to collect and analyze site data in such a way that the results can be presented as valid probability distributions. As in all environmental risk assessments, it already is known that uncertainty about the numerical results is generally large (i.e., on the range of at least an order of magnitude or greater). Consequently, it is more important to identify the key site-related variables and assumptions that contribute most to the uncertainty than to precisely quantify the degree of uncertainty in the risk assessment. Thus, the focus of this section is on qualitative/semi-quantitative approaches that can yield useful information to decision-makers for a limited resource investment.

There are several categories of uncertainties associated with site risk assessments. One is the initial selection of substances used to characterize exposures and risk on the basis of the sampling data and available toxicity information. Other sources of uncertainty are inherent in the toxicity values for each substance used to characterize risk. Additional uncertainties are inherent in the exposure assessment for individual substances and individual exposures. These uncertainties are usually driven by uncertainty in the chemical monitoring data and the models used to estimate exposure concentrations in the absence of monitoring data, but can also be driven by population intake parameters. Finally, additional uncertainties are incorporated in the risk assessment when exposures to several substances across multiple pathways are summed.

The following subsections describe how to summarize and discuss important site-specific exposure uncertainties and the more general toxicity assessment uncertainties.

8.4.1 IDENTIFY AND EVALUATE IMPORTANT SITE-SPECIFIC UNCERTAINTY FACTORS

Uncertainties in the exposure assessment typically include most of the site-specific uncertainties inherent in risk characterization, and thus are particularly important to summarize for each site. In risk assessments in general, and in the exposure assessment in particular, several sources of uncertainty need to be addressed: (1) definition of the physical setting, (2) model applicability and assumptions, (3) transport, fate, and exposure parameter values, and (4) tracking uncertainty, or how uncertainties are magnified through the various steps

of the assessment. Some of these sources of uncertainty can be quantified while others are best addressed qualitatively.

Definition of the physical setting. The initial characterization of the physical setting that defines the risk assessment for a Superfund site involves many professional judgments and assumptions. These include definition of the current and future land uses, identification of possible exposure pathways now and in the future, and selection of substances detected at the site to include in the quantitative risk assessment. In Superfund risk assessments, particular attention should be given to the following aspects of the definition of the physical setting.

- Likelihood of exposure pathways and land uses actually occurring. A large part of the risk assessment is the estimation of cancer risks or hazard indices that are conditional on the existence of the exposure conditions analyzed; e.g., if a residential development is built on the site 10 years from now, the health risks associated with contaminants from the site would be X. It is important to provide the RPM or other risk manager with information related to the likelihood that the assumed conditions will occur to allow interpretation of a conditional risk estimate in the proper context. For example, if the probability that a residential development would be built on the site 10 or 50 years from now is very small, different risk management decisions might be made than if the probability is high. Present the information collected during scoping and for the exposure assessment that will help the RPM to identify the relative likelihood of occurrence of each exposure pathway and land-uses, at least qualitatively (e.g., institutional land-use controls, zoning, regional development plans).

- The chemicals not included in the quantitative risk estimate as a consequence of missing information on health effects or lack of quantitation in the chemical analysis may represent a significant source of uncertainty in the final risk estimates. If chemicals with known health effects were eliminated from the risk assessment on the basis of concentration or frequency of detection, one should now review and confirm whether or not any of the chemicals previously eliminated should actually be included. For substances detected at the site, but not included in the quantitative risk assessment because of data limitations, discuss possible consequences of the exclusion on the risk assessment.

A checklist of uncertainty factors related to the definition of the physical setting is described in the box below.

LIST PHYSICAL SETTING DEFINITION UNCERTAINTIES

- For chemicals not included in the quantitative risk assessment, describe briefly:
  - reason for exclusion (e.g., quality control), and
  - possible consequences of exclusion on risk assessment (e.g., because of widespread contamination, underestimate of risk).
- For the current land uses describe:
  - sources and quality of information, and.
  - qualitative confidence level.
- For the future land uses describe:
  - sources and quality of information, and
  - information related to the likelihood of occurrence.
- For each exposure pathway, describe why pathway was selected or not selected for evaluation (i.e., sample table format from Exhibit 6-8).
- For each combination of pathways, describe any qualifications regarding the selection of exposure pathways considered to contribute to exposure of the same individual or group of individuals over the same period of time.

Model applicability and assumptions. There is always some doubt as to how well an exposure model or its mathematical expression (e.g., ground-water transport model) approximates the true relationships between site-specific environmental conditions. Ideally, one would like to use a fully validated model that accounts for all the known complexities in the parameter interrelationships for each assessment. At present, however, only simple, partially validated models are available and commonly used. As a consequence, it is important to identify key model assumptions (e.g., linearity, homogeneity, steady-state conditions, equilibrium) and their potential impact on

the risk estimates. In the absence of field data for model validation, one could perform a limited sensitivity analysis (i.e., vary assumptions about functional relationships) to indicate the magnitude of uncertainty that might be associated with model form. At a minimum, one should list key model assumptions and indicate potential impact of each on risk with respect to both direction and magnitude, as shown in the box below. A sample table format is presented in Exhibit 6-21 of Chapter 6.

CHARACTERIZE MODEL UNCERTAINTIES

- List/summarize the key model assumptions.
- Indicate the potential impact of each on risk:
  - direction (i.e., may over- or underestimate risk); and
  - magnitude (e.g., order of magnitude).

Parameter value uncertainty. During the course of a risk assessment, numerous parameter values are included in the calculations of chemical fate and transport and human intake. A first step in characterizing parameter value uncertainty in the baseline risk assessment is to identify the key parameters influencing risk. This usually can be accomplished by expert opinion or by an explicit sensitivity analysis. In a sensitivity analysis, the values of parameters suspected of driving the risks are varied and the degree to which changes in the input variables result in changes in the risk estimates are summarized and compared (e.g., the ratio of the change in output to the change in input). It is important to summarize the uncertainty associated with key parameters, as described below.

- Significant site data gaps might have required that certain parameter values be assumed for the risk assessment. For example, no information on the frequency with which individuals swim in a nearby stream might be available for a site, and an assumed frequency and duration of swimming events based on a national average could have driven the exposure estimate for this pathway.
- Significant data uncertainties might exist for other parameters, for example, whether or not the available soil concentration measurements are representative of the true distribution of soil contaminant concentrations.

Tracking uncertainty. Ideally, one would like to carry through the risk assessment the uncertainty associated with each parameter in order to characterize the uncertainty associated with the final risk estimates. A more practical approach for Superfund risk assessments is to describe qualitatively how the uncertainties might be magnified or biased through the risk models used. General quantitative, semi-quantitative, and qualitative approaches to uncertainty analysis are described below.

Quantitative approach. Only on the rare occasions that an RPM may indicate the need for a quantitative uncertainty analysis should one be undertaken. As mentioned earlier, a highly quantitative statistical uncertainty analysis is usually not practical or necessary for Superfund sites.

If a quantitative analysis is undertaken for a site, it is necessary to involve a statistician in the design and interpretation of that analysis. A quantitative approach to characterizing uncertainty might be appropriate if the exposure models are simple and the values for the key input parameters are well known. In this case, the first step would be to characterize the probability distributions for key input parameter values (either using measured or assumed distributions). The second step would be to propagate parameter value uncertainties through the analysis using analytic (e.g., first-order Taylor series approximation) or numerical (e.g., Monte Carlo simulation) methods, as appropriate. Analytic methods might be feasible if there are a few parameters with known distributions and linear relationships. Numerical methods (e.g., Monte Carlo simulation) can be suitable for more complex relationships, but must be done on a computer and can be resource intensive even with time-saving techniques (e.g., Latin Hypercube sampling).

Two common techniques of propagating uncertainty are first-order analyses and Monte Carlo simulations. First-order analysis is based on the assumption that the total variance of a model output variable is a function of the variances of the individual model input variables and the sensitivity of the output variable to changes in input variables. The sensitivity of the output variable is defined by the first derivative of the function or model, which can be generated analytically or numerically. A Monte Carlo simulation estimates a distribution of exposures or risk by repeatedly solving the model equation(s). The probability distribution for each variable in the model must be defined. The computer selects randomly from each distribution every time the equation is solved. From the resulting output distribution of exposures or risk, the assessor can identify the value corresponding to any specified percentile (e.g., the 95th percentile in the exposure distribution).

These quantitative techniques require definition of the distribution of all input parameters and knowledge of the degree of dependence (i.e., covariance) among parameters. The value of first-order analyses or Monte Carlo simulations in estimating exposure or risk probability distributions diminishes sharply if one or more parameter value distributions are poorly defined or must be assumed. These techniques also become difficult to document and to review as the number of model parameters increases. Moreover, estimating a probability distribution for exposures and risks can lead one into a false sense of certainty about the analysis. Even in the most comprehensive analyses, it will generally be true that not all of the sources of uncertainty can be accounted for or all of the parameter codependencies recognized. Therefore, in addition to documenting all input distributions and covariances, it is very important to identify all of the assumptions and incomplete information that have not been accounted for in the quantitative uncertainty analysis (e.g., likelihood that a particular land use will occur) when presenting the results.

References describing numerical methods of propagating uncertainty through a risk analysis include Burmaster and von Stackelberg (1988), Hoffman and Gardner (1983), Iman and Helton (1988), and NRC (1983). References describing analytic methods of tracking uncertainty include Hoffman and Gardner (1983), NRC (1983), Downing *et al*. (1985), and Benjamin and Cornell (1970).

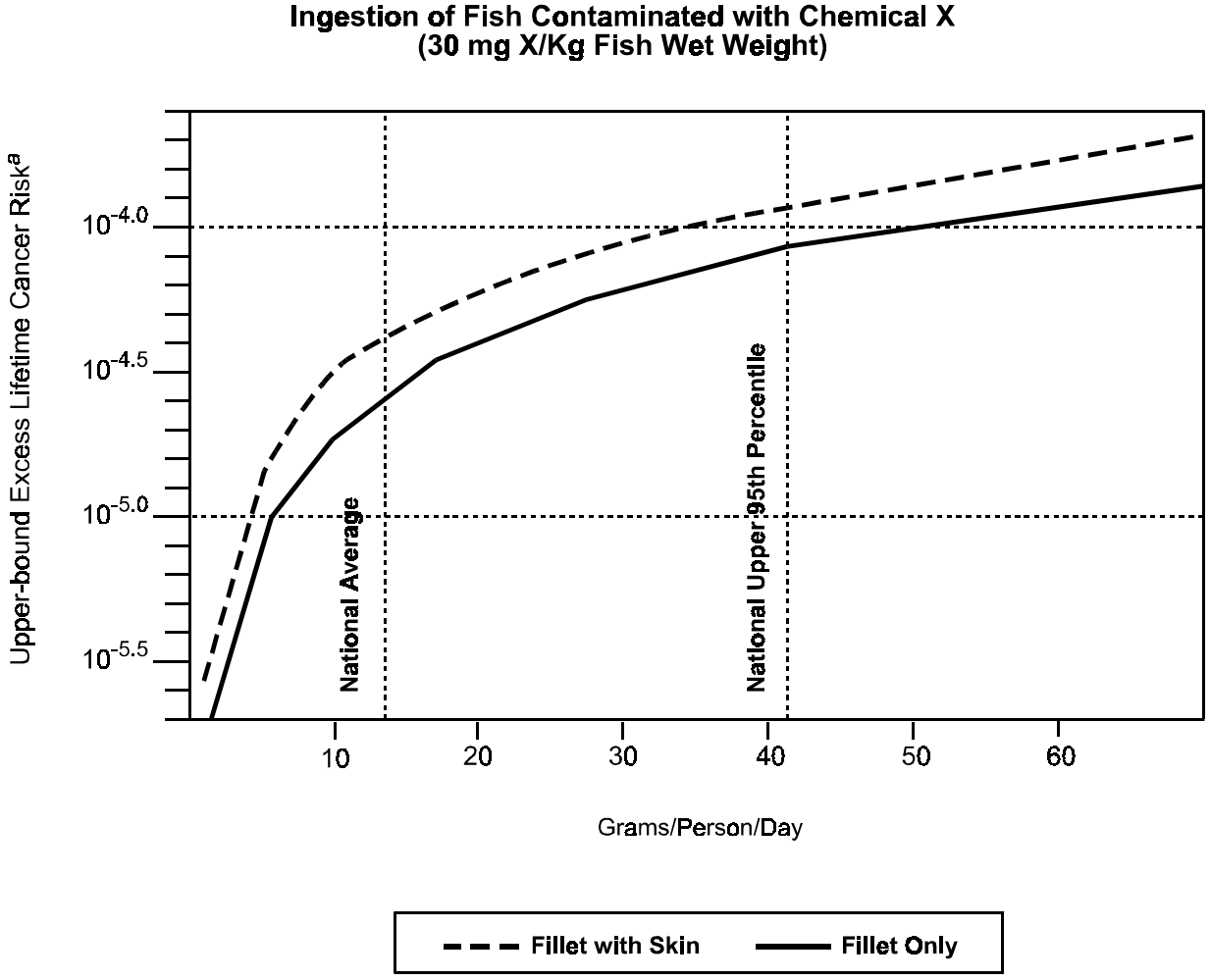
Semi-quantitative approach. Often available data are insufficient to fully describe parameter distributions, but are sufficient to describe the potential range of values the parameters might assume. In this situation, sensitivity analyses can be used to identify influential model input variables and to develop bounds on the distribution of exposure or risk. A sensitivity analysis can estimate the range of exposures or risk that result from combinations of minimum and maximum values for some parameters and mid-range values for others. The uncertainty for an assessment of this type could be characterized by presenting the ranges of exposure or risk generated by the sensitivity analysis and by describing the limitations of the data used to estimate plausible ranges of model input variables (EPA 1985).

Qualitative approach. Sometimes, a qualitative approach is the most practical approach to describing uncertainty in Superfund site risk assessments given the use of the information (e.g., identifying areas where the results may be misleading). Often the most practical approach to characterizing parameter uncertainty will be to develop a quantitative or qualitative description of the uncertainty for each parameter and to simply indicate the possible influence of these uncertainties on the final risk estimates given knowledge of the models used (e.g., a specific ground-water transport model). A checklist of uncertainty factors related to the definition of parameters is described in the box on page 8-22. A sample table format is provided in Exhibit 6-21 of Chapter 6.

Consider presentation of information on key parameter uncertainties in graphic form to illustrate clearly to the RPM or other risk managers the significance of various assumptions. For example, Exhibit 8-5 plots assumptions regarding contaminated fish ingestion and resulting impacts on the cancer risk estimate for this exposure pathway. Exhibit 8-6 illustrates the significance of these same assumptions for the hazard index estimates for contaminated fish consumption. Additionally, maps showing isopleths of risks resulting from modeled air exposures such as emissions near the site may assist the RPM or risk manager in visualizing the significance of current or future site risks for a community.

EXHIBIT 8-5

EXAMPLE OF PRESENTATION OF IMPACT OF EXPOSURE ASSUMPTIONS ON CANCER RISK ESTIMATE



[a] The risk of developing cancer is plotted on a log scale. A risk of 10^{-4} indicates a probability of 1 chance in 10,000 and a risk of 10^{-5} indicates a probability of 1 chance in 100,000 of an individual developing cancer.

CHARACTERIZE FATE AND TRANSPORT AND EXPOSURE PARAMETER UNCERTAINTIES

- List all key exposure assessment parameters (e.g., infiltration rate, exposure duration, bioconcentration factors, body weight).
- List the value used for each parameter and rationale for its selection.
- Describe the measured or assumed parameter value distributions, if possible, considering:
  - total range;
  - shape of distribution, if known (e.g., log-normal);
  - mean (geometric or arithmetic) + standard deviation; and/or
  - specific percentiles (e.g., median, 95th).
- Quantify the uncertainty of statistical values used in the risk assessment (e.g., standard error of the mean) or data gaps and qualifiers.
- Describe potential direction and magnitude of bias in risk estimate resulting from assumptions or data gaps (see Exhibit 6-21).

8.4.2 IDENTIFY/EVALUATE TOXICITY ASSESSMENT UNCERTAINTY FACTORS

For substances that contribute most to the estimates of cancer risk and noncancer hazard indices, summarize the uncertainty inherent in the toxicity values for the durations of exposure assessed. Some of the information (e.g., weight of evidence for potential human carcinogens, uncertainty adjustments for noncancer toxicity values) has already been recorded in the sample table formats provided in Exhibits 8-2 through 8-4. Other information will be developed during the toxicity assessment itself (see Chapter 7). The box on page 8-24 provides a checklist of uncertainties that apply to most toxicity assessments.

Multiple substance exposure uncertainties. Uncertainties associated with summing risks or hazard indices for several substances are of particular concern in the risk characterization step. The assumption of dose additivity ignores possible synergisms or antagonisms among chemicals, and assumes similarity in mechanisms of action and metabolism. Unfortunately, the data available to assess interactions quantitatively are generally lacking. In the absence of adequate information, EPA guidelines indicate that carcinogenic risks should be treated as additive and that noncancer hazard indices should also be treated as additive. These assumptions are made to help prevent an underestimation of cancer risk or potential noncancer health effects at a site.

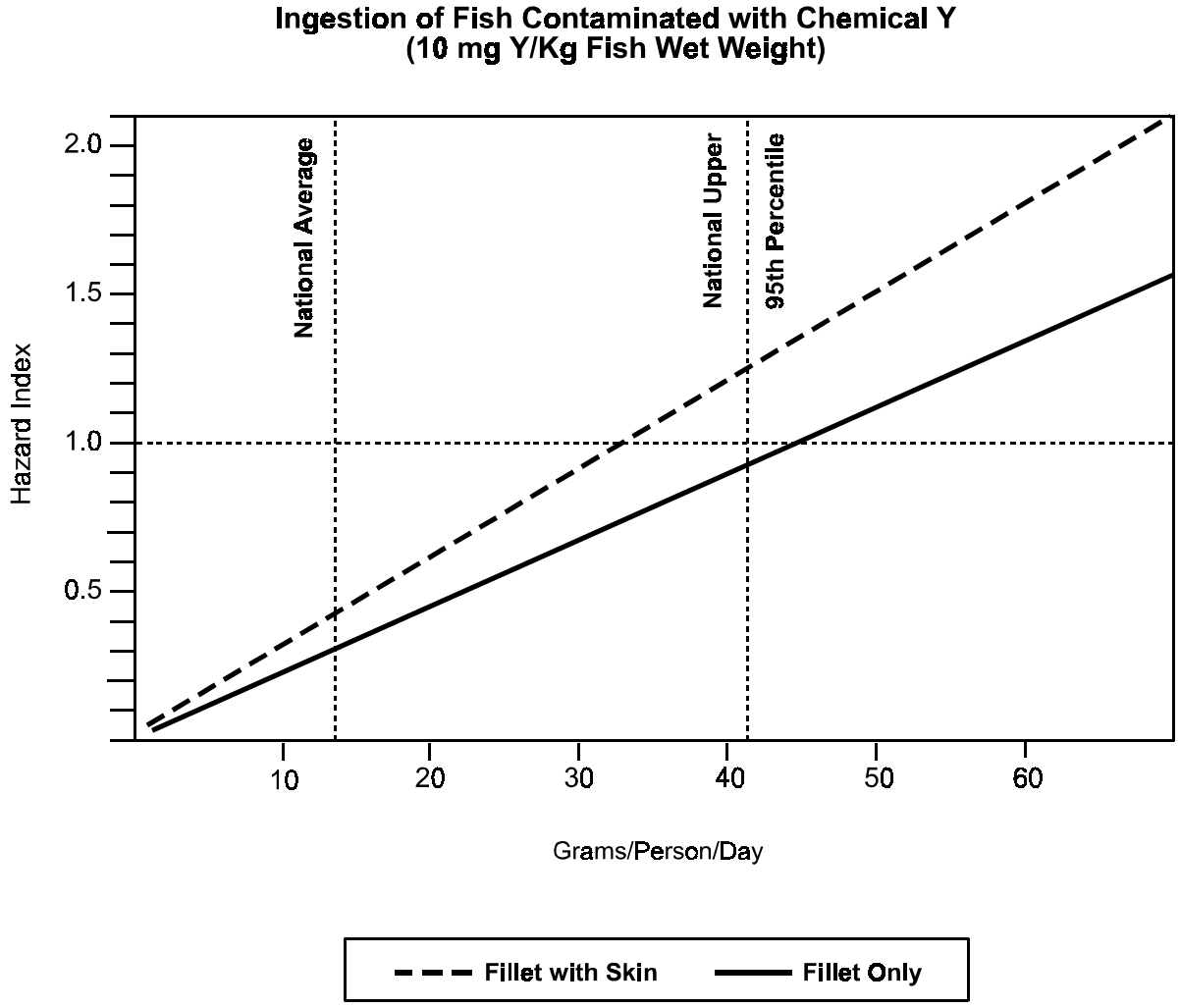
Be sure to discuss the availability of information concerning potential antagonistic or synergistic effects of chemicals for which cancer risks or hazard indices have been summed for the same exposed individual or subpopulations. On the basis of available information concerning target organ specificity and mechanism of action, indicate the degree to which treating the cancer risks as additive may over- or under-estimate risk. If only qualitative information is available concerning potential interactions or dose-additivity for the noncarcinogenic substances, discuss whether the information indicates that hazard indices may have been over- or under-estimated. This discussion is particularly important if the total hazard index for an exposure point is slightly below or slightly above unity, or if the total hazard index exceeds unity and the effect-specific hazard indices are less than unity, and if the uncertainty is likely to significantly influence the risk management decision at the site.

8.5 CONSIDERATION OF SITE-SPECIFIC HUMAN STUDIES

This section describes how to compare the results of the risk characterization step with ATSDR health assessments and other site-specific human studies that might be available. The first subsection outlines how to compare an ATSDR health assessment for the site with the risk results summarized in the previous sections (Sections 8.2, 8.3, and 8.4). The second subsection discusses when epidemiological or health studies might provide useful information for assessing exposures and health risks associated with contaminants from a site.

EXHIBIT 8-6

EXAMPLE OF PRESENTATION OF IMPACT OF EXPOSURE ASSUMPTIONS ON HAZARD INDEX ESTIMATE



CHARACTERIZE TOXICITY ASSESSMENT UNCERTAINTIES

For each substance carried through the quantitative risk assessment, list uncertainties related to:

- qualitative hazard findings (i.e., potential for human toxicity);
- derivation of toxicity values, e.g.,
  - human or animal data,
  - duration of study (e.g., chronic study used to set subchronic RfD), and
  - any special considerations;
- the potential for synergistic or antagonistic interactions with other substances affecting the same individuals; and
- calculation of lifetime cancer risks on the basis of less-than-lifetime exposures.

For each substance not included in the quantitative risk assessment because of inadequate toxicity information, list:

- possible health effects; and
- possible consequences of exclusion on final risk estimates.

8.5.1 COMPARE WITH ATSDR HEALTH ASSESSMENT

ATSDR health assessments were defined and compared to the RI/FS risk assessment in Section 2.2.2. As of 1989, preliminary ATSDR health assessments should be completed before the RI/FS risk assessment is initiated and therefore should be available to the risk assessor as early as "scoping." The steps for comparing the preliminary ATSDR health assessment with the baseline risk assessment are outlined below.

Review again the ATSDR health assessment findings and conclusions. These will be largely qualitative in nature. If the ATSDR health assessment identifies exposure pathways or chemicals of concern that have not been included in the RI/FS baseline risk assessment, describe the information supporting the decision not to include these parameters. If there are differences in the qualitative conclusions of the health assessment and the quantitative conclusions of the baseline risk assessment, explain the differences, if possible, and discuss their implications.

8.5.2 COMPARE WITH OTHER AVAILABLE SITE-SPECIFIC EPIDEMIOLOGICAL OR HEALTH STUDIES

For most Superfund sites, studies of human exposure or health effects in the surrounding population will not be available. However, if controlled epidemiological or other health studies have been conducted, perhaps as a consequence of the preliminary ATSDR health assessment or other community involvement, it is important to include this information in the baseline risk assessment as appropriate. However, not all such studies provide meaningful information in the context of Superfund risk assessments.

One can determine the availability of other epidemiological or health studies for populations potentially exposed to contaminants from the site by contacting the ATSDR Regional Representative, the Centers for Disease Control in Atlanta, Georgia, and state and local health agencies as early in the risk assessment process as possible. It is important to avoid use of anecdotal information or data from studies that might include a significant bias or confounding factor, however. Isolated reports of high body levels of substances that are known to be present at the site in a few individuals living near the site are not sufficient evidence to confirm the hypothesis that these individuals have received significant exposures from the site. Nor can isolated reports of disease or symptoms in a few individuals living near the site be used to confirm the hypothesis that the cause of the health effects in these individuals was exposure to contamination from the site. A trained epidemiologist should review any available studies in order to identify possible study limitations and implications for site risk findings. The small populations and variable exposures predominating at most Superfund sites will make it extremely difficult to detect site-related effects using epidemiological techniques.

If site-specific health or exposure studies have been identified and evaluated as adequate, one should incorporate the study findings into the overall

risk characterization to strengthen the conclusions of the risk assessment (e.g., the risk assessment predicts elevated blood lead levels and the human exposure study documented elevated blood lead levels only among those exposed to ground water contaminated by the site). Because of the generally large and different types of uncertainties associated with the risk assessment and actual health studies, a qualitative, not quantitative, comparison between the two types of studies is generally warranted. Areas of agreement and disagreement between the health study(ies) and the risk assessment should be described and factors that might contribute to any disagreement discussed.

8.6 SUMMARIZATION AND PRESENTATION OF THE BASELINE RISK CHARACTERIZATION RESULTS

This section provides guidance on interpreting and presenting the risk characterization results. The results of the baseline evaluation should not be taken as a characterization of absolute risk. An important use of the risk and hazard index estimates is to highlight potential sources of risk at a site so that they may be dealt with effectively in the remedial process. It is the responsibility of the risk assessment team to develop conclusions about the magnitude and kinds of risk at the site and the major uncertainties affecting the risk estimates. It is not the responsibility of the risk assessment team to evaluate the significance of the risk in a program context, or whether and how the risk should be addressed, which are risk management decisions.

The ultimate user of the risk characterization results will be the RPM or other risk manager for the site. This section therefore outlines a presentation of material that is designed to assist the risk manager in using risk information to reach site-specific decisions.

8.6.1 SUMMARIZE RISK INFORMATION IN TEXT

The final discussion of the risk characterization results is a key component of the risk characterization. The discussion provides a means of placing the numerical estimates of risk and hazard in the context of what is known and what is not known about the site and in the context of decisions to be made about selection of remedies. At a minimum, the discussion should include:

- confidence that the key site-related contaminants were identified and discussion of contaminant concentrations relative to background concentration ranges;
- a description of the various types of cancer and other health risks present at the site (e.g., liver toxicity, neurotoxicity), distinguishing between known effects in humans and those that are predicted to occur based on animal experiments;
- level of confidence in the quantitative toxicity information used to estimate risks and presentation of qualitative information on the toxicity of substances not included in the quantitative assessment;
- level of confidence in the exposure estimates for key exposure pathways and related exposure parameter assumptions;
- the magnitude of the cancer risks and noncancer hazard indices relative to the Superfund site remediation goals in the NCP (e.g., the cancer risk range of 10^{-4} to 10^{-7} and noncancer hazard index of 1.0);
- the major factors driving the site risks (e.g., substances, pathways, and pathway combinations);
- the major factors reducing the certainty in the results and the significance of these uncertainties (e.g., adding risks over several substances and pathways);
- exposed population characteristics; and
- comparison with site-specific health studies, when available.

In addition, if the size of the potentially exposed population is large, the presentation of population numbers may be of assistance to the RPM, especially in evaluating risks in the context of current land use.

Individual risk estimates based on the reasonable maximum exposure (RME) should not be presented as representative of a broadly defined population, however.

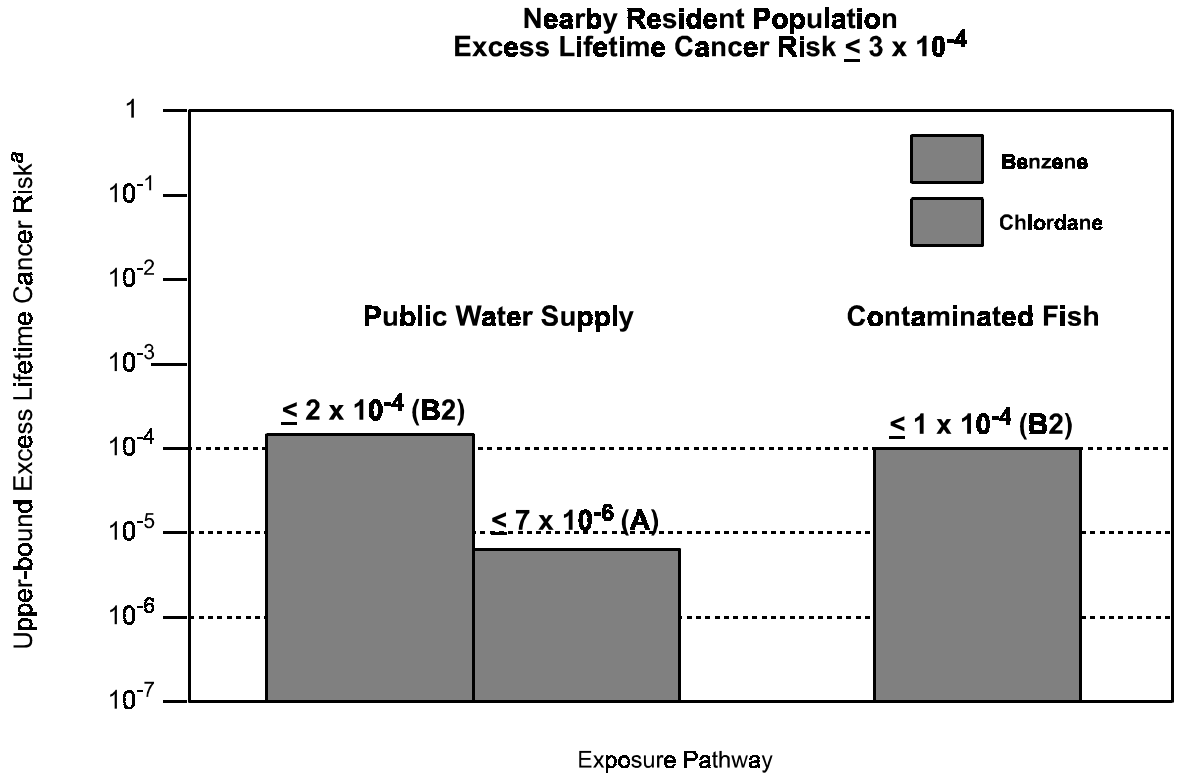
8.6.2 SUMMARIZE RISK INFORMATION IN TABLES

A tabular summary of the cancer risks and noncancer hazard indices should be prepared for all exposure pathways and land uses analyzed and for all substances carried through the risk assessment. These tables must be accompanied by explanatory text, as described in the previous section, and should not be allowed to stand alone as the entire risk characterization. The sample table formats presented in Chapter 6 and in Exhibits 8-2 to 8-6 provide basic summary formats. Exhibits 8-7 and 8-8 provide examples of optional presentations that might assist in visualization of the risk assessment results. These bar graphs present the baseline cancer risk estimates and noncancer hazard indices, respectively, by pathway for an identified subpopulation near the site. The stacked bars in Exhibit 8-8 allow the reader to immediately identify the pathway(s) contributing most to the total hazard index as well as identify the substances driving the indices in each pathway. Reference levels are also provided (e.g., hazard index of 1.0). Exhibits 8-5 and 8-6 introduced in Section 8.4.1 provide examples of figures that could help the RPM or other risk manager visualize the impact of various assumptions and uncertainties on the final risk or hazard index estimate. In addition, graphics relating risk level (or magnitude of hazard index) to concentrations of substances in environmental media and cost of "treatment" could allow the RPM or other risk manager to weigh the benefits of various remedial alternatives more easily. Examples of the last type of graphics are presented in Part C of this manual.

In a few succinct concluding paragraphs, summarize the results of the risk characterization step. It is the responsibility of the risk assessment team members, who are familiar with all steps in the site risk assessment, to highlight the major conclusions of the risk assessment. The discussion should summarize both the qualitative and the quantitative findings of cancer risks and noncancer hazards, and properly qualify these by mention of major assumptions and uncertainties in the assessment.

EXHIBIT 8-7

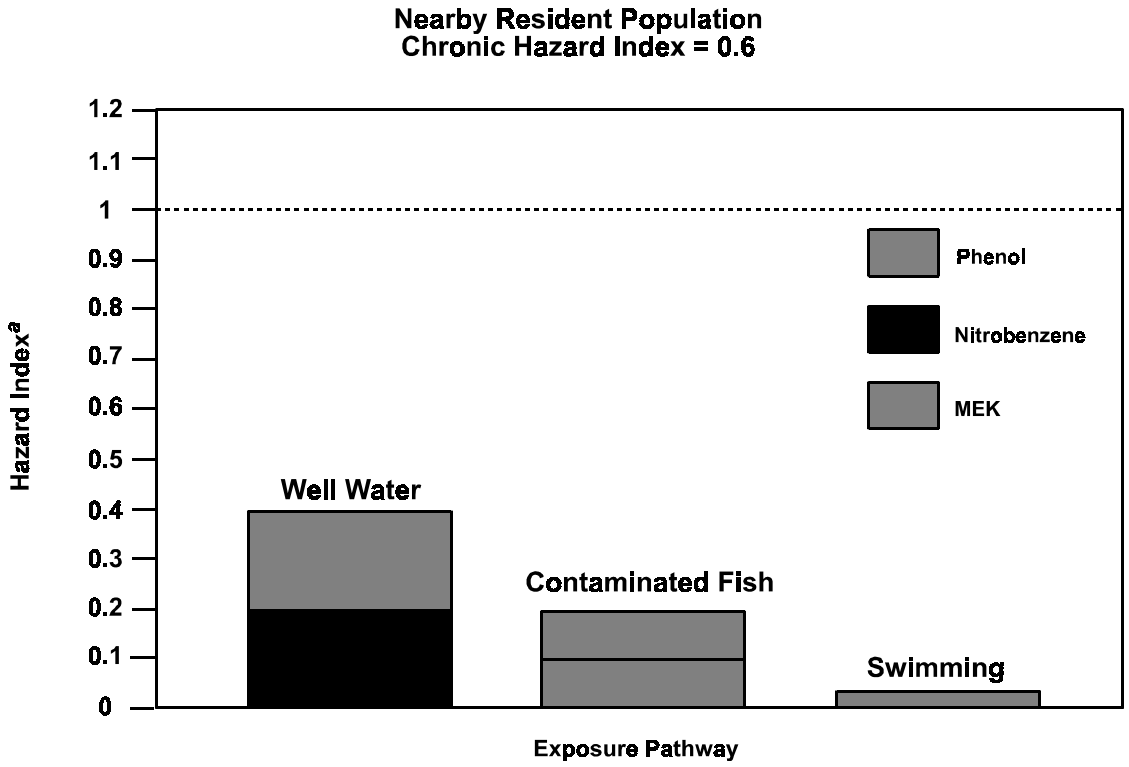
EXAMPLE OF PRESENTATION OF RELATIVE CONTRIBUTION OF INDIVIDUAL CHEMICALS TO EXPOSURE PATHWAY AND TOTAL CANCER RISK ESTIMATES



[a] The risk of developing cancer is plotted on a log scale. A risk of 10^{-4} indicates a probability of 1 chance in 10,000 of an individual developing cancer. Risks of 10^{-5} and 10^{-6} correspond to probabilities of 1 chance in 100,000 and 1 chance in 1,000,000 respectively. Values in parentheses represent EPA's weight-of-evidence classification of the agent as a potential human carcinogen: A = human carcinogen; and B2 = probable human carcinogen (with sufficient evidence in animals and inadequate or no evidence in humans).

EXHIBIT 8-8

EXAMPLE OF PRESENTATION OF RELATIVE CONTRIBUTION OF INDIVIDUAL CHEMICALS TO EXPOSURE PATHWAY AND TOTAL HAZARD INDEX ESTIMATES



[a] The hazard index is equal to the sum of the hazard quotients (i.e., exposure level/RfD) for each chemical. It is not a probability; a hazard index or quotient of ≤ 1.0 indicates that it is unlikely for even sensitive populations to experience adverse health effects.

ENDNOTE FOR CHAPTER 8

1. The probability of an individual developing cancer following exposure to more than one carcinogen is the probability of developing cancer from *at least one* of the carcinogens. For two carcinogens, the precise equation for estimating this probability is $risk_1 + risk_2$ -probability ($risk_1$, $risk_2$) where the latter term is the joint probability of the two risks occurring in the same individual. If the risk to agent 1 is distributed in the population independently of the risk to agent 2, the latter term would equal ($risk_1$)($risk_2$). This equation can be expanded to evaluate risks from more than two substances.

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CHAPTER 9

DOCUMENTATION, REVIEW, AND MANAGEMENT TOOLS FOR THE ASSESOR, REVIEWER, AND MANAGER

This chapter provides tools for the documentation, review, and management of the baseline risk assessment. These tools will help ensure completeness and consistency throughout the risk assessment and in the reporting of assessment results. Section 9.1 provides documentation tools (for risk assessors), Section 9.2 provides review tools (for risk assessment reviewers), and Section 9.3 provides management tools (for remedial project managers [RPMs] and other decision-makers concerned with the site).

9.1 DOCUMENTATION TOOLS

Throughout Chapters 4 to 8 of this manual, guidance is provided to the risk assessor on how to summarize and document many beginning, intermediate, and final steps of the risk assessment. The purpose of this section is to consolidate that guidance, provide a final check to ensure that all appropriate documentation has been completed, and provide additional information that should be helpful. This section addresses (1) basic principles of documenting a Superfund site risk assessment (e.g., key "dos" and don'ts", the rationale for consistency), (2) a suggested outline and guidance for the risk assessment report, and (3) guidance for providing risk assessment summaries in other key reports.

9.1.1 BASIC PRINCIPLES

There are three basic principles for documenting a baseline risk assessment:

(1) address the main objectives of the risk assessment;

(2) communicate using clear, concise, and relevant text, graphics, and tables; and

(3) use a consistent format.

Addressing the objectives. The objectives of the baseline risk assessment -- to help determine whether additional response action is necessary at the site, to provide a basis for determining residual chemical levels that are adequately protective of public health, to provide a basis for comparing potential health impacts of various remedial alternatives, and to help support selection of the "no-action" remedial alternative (where appropriate) -- should be considered carefully during the documentation of the risk assessment. Recognizing these objectives early and presenting the results of the risk assessment with them in mind will assist the RPM and other decision-makers at the site with readily obtaining and using the necessary information to evaluate the objectives. Failing to recognize the importance of the objectives could result in a risk assessment report that appears misdirected and/or unnecessary.

Communicating. Clearly and concisely communicating the relevant results of the risk assessment can be one of the most important aspects of the entire RI/FS. If done correctly, a useful instrument for mitigating public health threats will have been developed. If done incorrectly, however, risks could be underemphasized, possibly leading to the occurrence of adverse health effects, or they could be overemphasized, possibly leading to the unnecessary expenditure of limited resources. See

the box below for some helpful hints on communicating the baseline risk assessment.

HELPFUL HINTS: COMMUNICATING THE BASELINE RISK ASSESSMENT

Try to:

- use a mix of well written text, illustrative graphics, and summary tables;
- explain the major steps and the results of the risk assessment in terms easily understood by the general public (and especially by members of exposed or potentially exposed populations);
- define highly technical terms early (e.g., in a glossary); and
- use a standard quantitative system -- preferably the metric system -- throughout and units that are the same where possible (e.g., ug/L for all water concentrations).

Avoid:

- the use of large blocks of text unbroken by any headings, graphics, tables, lists, or other "visual dividers";
- the presentation of much quantitative information within the text (rather than in tables); and
- the drawing of "risk management" conclusions (e.g., stating that the total or largest risk is insignificant).

Many skills for communicating the baseline risk assessment also can be learned by reviewing the literature on risk communication. The following box lists just some of the literature that is available. Courses on the subject also exist.

RISK COMMUNICATION GUIDANCE

Explaining Environmental Risk (EPA 1986)

Tools for Environmental Professionals Involved in Risk Communication At Hazardous Waste Facilities Undergoing Siting, Permitting, or Remediation (Bean 1987)

Improving Dialogue with Communities: A Short Guide for Government Risk Communication (NJDEP 1987)

Seven Cardinal Rules of Risk Communication (EPA 1988a)

Using a consistent format. A consistent format for all Superfund risk assessments is strongly recommended for four important reasons:

(1) it encourages consistency and completeness in the assessment itself;

(2) it allows for easier review of the risk assessments;

(3) it encourages consistent use of the results by RPMs and other decision-makers; and

(4) it helps demonstrate to the public and others that risk assessments are conducted using the same framework (if not the same specific procedures).

Using other formats can lead to slower review times, different interpretations of similar results, and the charge that risk assessments are inappropriately being conducted differently from one site to another. The following subsections provide guidance on the use of consistent formats.

9.1.2 BASELINE RISK ASSESSMENT REPORT

The baseline risk assessment report references and supports the RI/FS report. Depending on the site, the risk assessment report can range from a small, simple document with no appendices that can simply be added to the RI/FS report as a chapter, to a large, complex document with many appendices that can "stand alone." This subsection provides general guidance on how to organize the baseline risk assessment report and which information should be included in the report. More detailed guidance, however, is found by following the guidance in previous chapters of this manual. Careful use of that guidance will ensure a well-documented baseline risk assessment report.

Exhibit 9-1 provides a suggested outline for the full baseline risk assessment report. This outline generally follows the flow of the risk assessment and the organization of this manual. The "bulleted" items are not necessarily section headings, but rather are often items that should be considered when writing the report. Note that, as with the manual, not all components of the outline are applicable to all sites. This is especially true if the risk assessment report will be a chapter in the RI/FS report. At some sites, and especially when the risk assessment report will be a stand-alone document, more site-specific items could be added to the report.

Examples of tables and graphics that should be included in the report are presented as exhibits in previous chapters of this manual. Note, however, that additional tables and graphics may be useful.

This suggested outline may be used as a review guide by risk assessors (and risk assessment reviewers) to ensure that all appropriate components of the assessment have been addressed. Section 9.2 addresses review tools in greater detail.

9.1.3 OTHER KEY REPORTS

Two important reports that must include summaries of the baseline risk assessment are (1) the remedial investigation/feasibility study (RI/FS) report and (2) the record of decision (ROD) report.

Summary for the RI/FS report. One of the chapters of the RI/FS typically is devoted to a summary of the baseline risk assessment. Part of this summary should address the human health evaluation (the other part should address the environmental evaluation). The human health summary should follow the same outline as the full baseline risk assessment report, with almost each section of the summary being a distillation of each full report chapter. The risk characterization chapter is an exception, however, in that it could be included in the RI/FS report essentially unchanged. Most tables and graphics should be included unchanged as well. For more information, see *Guidance for Conducting Remedial Investigations and Feasibility Studies Under CERCLA* (EPA 1988b).

Summary for the ROD report. The ROD documents the remedial action selected for a site. It consists of three basic components: (1) a Declaration; (2) a Decision Summary; and (3) a Responsiveness Summary. The second component, a Decision Summary, provides an overview of the site-specific factors and analyses that led to the selection of the remedy. Included in this component is a summary of site risks. As with the risk assessment summary for the RI/FS report, the summary for the ROD report should follow the same outline as the full risk assessment. This summary, however, should be much more abbreviated than the RI/FS summary, although care must be taken to address all of the relevant site-specific results. For more information, see *Interim Final Guidance on Preparing Superfund Decision Documents: The Proposed Plan, the Record of Decision, Explanation of Significant Differences, and the Record of Decision Amendment* (EPA 1989).

9.2 REVIEW TOOLS

This section provides guidelines on reviewing a risk assessment report. A checklist of many essential criteria that should be adequately addressed in any good risk assessment is provided (Exhibit 9-2). The checklist touches upon issues that are often problematic and lead to difficulty and delay in the review of risk assessments. Principal questions are presented in the checklist with qualifying statements or follow-up questions, as well as references to appropriate chapters and sections of this manual. The checklist is intended as a guide to assist the preliminary reviewer by ensuring that critical issues concerning the quality and adequacy of information are not overlooked at the screening level review of risk assessments. Experience has shown that reviewers should pay particular attention to the following concerns.

- Were all appropriate media sampled?
- Were any site-related chemicals (e.g., human carcinogens) eliminated from analysis without appropriate justification?

EXHIBIT 9-1

SUGGESTED OUTLINE FOR A BASELINE RISK ASSESSMENT REPORT

1.0 INTRODUCTION

1.1 Overview
- General problem at site
- Site-specific objectives of risk assessment

1.2 Site Background
- Site description
- Map of site
- General history
  -- Ownership
  -- Operations
  -- Contamination
- Significant site reference points
- Geographic location relative to offsite areas of interest
- General sampling locations and media

1.3 Scope of Risk Assessment
- Complexity of assessment and rationale
- Overview of study design

1.4 Organization of Risk Assessment Report

2.0 IDENTIFICATION OF CHEMICALS OF POTENTIAL CONCERN

2.1 General Site-specific Data Collection Considerations
- Detailed historical information relevant to data collection
- Preliminary identification of potential human exposure
- Modeling parameter needs
- Background sampling
- Sampling locations and media
- Sampling methods
- QA/QC methods
- Special analytical services (SAS)

2.2 General Site-specific Data Evaluation Considerations
- Steps used (including optional screening procedure steps, if used)
- QA/QC methods during evaluation
- General data uncertainty

2.3 Environmental Area or Operable Unit 1 (Complete for All Media)
- Area- and media-specific sample collection strategy (e.g., sample size, sampling locations)
- Data from site investigations

(continued)

EXHIBIT 9-1 (continued)

SUGGESTED OUTLINE FOR A BASELINE RISK ASSESSMENT REPORT

- Evaluation of analytical methods
- Evaluation of quantitation limits
- Evaluation of qualified and coded data
- Chemicals in blanks
- Tentatively identified compounds
- Comparison of chemical concentrations with background
- Further limitation of number of chemicals
- Uncertainties, limitations, gaps in quality of collection or analysis

2.4 Environmental Area or Operable Unit 2 (Repeat for All Areas or Operable Units, As Appropriate)

2.X Summary of Chemicals of Potential Concern

3.0 EXPOSURE ASSESSMENT

3.1 Characterization of Exposure Setting
- Physical Setting
  -- Climate
  -- Vegetation
  -- Soil type
  -- Surface hydrology
  -- Ground-water hydrology
- Potentially Exposed Populations
  -- Relative locations of populations with respect to site
  -- Current land use
  -- Potential alternate future land uses
  -- Subpopulations of potential concern

3.2 Identification of Exposure Pathways
- Sources and receiving media
- Fate and transport in release media
- Exposure points and exposure routes
- Integration of sources, releases, fate and transport mechanisms, exposure points, and exposure routes into complete exposure pathways
- Summary of exposure pathways to be quantified in this assessment

3.3 Quantification of Exposure
- Exposure concentrations
- Estimation of chemical intakes for individual pathways

(continued)

EXHIBIT 9-1 (continued)

SUGGESTED OUTLINE FOR A BASELINE RISK ASSESSMENT REPORT

3.4 Identification of Uncertainties
- Current and future land-use
- Environmental sampling and analysis
- Exposure pathways evaluated
- Fate and transport modeling
- Parameter values

3.5 Summary of Exposure Assessment

4.0 TOXICITY ASSESSMENT

4.1 Toxicity Information for Noncarcinogenic Effects
- Appropriate exposure periods for toxicity values
- Up-to-date RfDs for all chemicals
- One- and ten-day health advisories for shorter-term oral exposures
- Overall data base and the critical study on which the toxicity value is based (including the critical effect and the uncertainty and modifying factors used in the calculation)
- Effects that may appear at doses higher than those required to elicit the critical effect
- Absorption efficiency considered

4.2 Toxicity Information for Carcinogenic Effects
- Exposure averaged over a lifetime
- Up-to-date slope factors for all carcinogens
- Weight-of-evidence classification for all carcinogens
- Type of cancer for Class A carcinogens
- Concentration above which the dose-response curve is no longer linear

4.3 Chemicals for Which No EPA Toxicity Values Are Available
- Review by ECAO
- Qualitative evaluation
- Documentation/justification of any new toxicity values developed

4.4 Uncertainties Related to Toxicity Information
- Quality of the individual studies
- Completeness of the overall data base

4.5 Summary of Toxicity Information

5.0 RISK CHARACTERIZATION

5.1 Current Land-use Conditions
- Carcinogenic risk of individual substances
- Chronic hazard quotient calculation (individual substances)
- Subchronic hazard quotient calculation (individual substances)

(continued)

EXHIBIT 9-1 (continued)

SUGGESTED OUTLINE FOR A BASELINE RISK ASSESSMENT REPORT

- Shorter-term hazard quotient calculation (individual substances)
- Carcinogenic risk (multiple substances)
- Chronic hazard index (multiple substances)
- Subchronic hazard index (multiple substances)
- Shorter-term hazard index calculation (multiple substances)
- Segregation of hazard indices
- Justification for combining risks across pathways
- Noncarcinogenic hazard index (multiple pathways)
- Carcinogenic risk (multiple pathways)

5.2 Future Land-use Conditions

- Carcinogenic risk of individual substances
- Chronic hazard quotient calculation (individual substances)
- Subchronic hazard quotient calculation (individual substances)
- Carcinogenic risk (multiple substances)
- Chronic hazard index (multiple substances)
- Subchronic hazard index (multiple substances)
- Segregation of hazard indices
- Justification for combining risks across pathways
- Noncarcinogenic hazard index (multiple pathways)
- Carcinogenic risk (multiple pathways)

5.3 Uncertainties

- Site-specific uncertainty factors
  - -- Definition of physical setting
  - -- Model applicability and assumptions
  - -- Parameter values for fate/transport and exposure calculations
- Summary of toxicity assessment uncertainty
  - -- Identification of potential health effects
  - -- Derivation of toxicity value
  - -- Potential for synergistic or antagonistic interactions
  - -- Uncertainty in evaluating less-than-lifetime exposures

5.4 Comparison of Risk Characterization Results to Human Studies

- ATSDR health assessment
- Site-specific health studies (pilot studies or epidemiological studies)
- Incorporation of studies into the overall risk characterization

5.5 Summary Discussion and Tabulation of the Risk Characterization

- Key site-related contaminants and key exposure pathways identified
- Types of health risk of concern
- Level of confidence in the quantitative information used to estimate risk
- Presentation of qualitative information on toxicity

(continued)

EXHIBIT 9-1 (continued)

SUGGESTED OUTLINE FOR A BASELINE RISK ASSESSMENT REPORT

- Confidence in the key exposure estimates for the key exposure pathways
- Magnitude of the carcinogenic and noncarcinogenic risk estimates
- Major factors driving risk
- Major factors contributing to uncertainty
- Exposed population characteristics
- Comparison with site-specific health studies

6.0 SUMMARY

6.1 Chemicals of Potential Concern
6.2 Exposure Assessment
6.3 Toxicity Assessment
6.4 Risk Characterization

EXHIBIT 9-2

REVIEWER CHECKLIST

1.0 GENERAL CONCERNS

- Were the site-specific objective(s) of the risk assessment stated? (HHEM - 1)
- Was the scope of the assessment described (e.g., in terms of the complexity of the assessment and rationale, data needs, and overview of the study design)? (HHEM - 1.1.1, 3.5)
- Was an adequate history of site activities provided, including a chronology of land use (e.g., specifying agriculture, industry, recreation, waste deposition, and residential development at the site)? (HHEM - 2.1.4, 9.1)
- Was an initial qualitative overview of the nature of contamination included (e.g., specifying in a general manner the kinds of contaminants, media potentially contaminated)? (HHEM - 2.1.4, 9.1)
- Was a general map of the site depicting boundaries and surface topography included, which illustrates site features, such as fences, ponds, structures, as well as geographical relationships between specific potential receptors and the site? (HHEM - 2.1.4, 9.1)

2.0 CONCERNS IN REVIEWING DATA COLLECTION AND EVALUATION

2.1 Data Collection

- Was an adequate "conceptual model" of the site discussed? (HHEM - 4.2)
  - -- a qualitative discussion of potential or suspected sources of contamination, types and concentrations of contaminants detected at the site, potentially contaminated media, as well as potential exposure pathways and receptors
- Was an adequate Data Quality Objectives (DQO) statement provided? (HHEM - 4.1.4)
  - -- a statement specifying both the qualitative and quantitative nature of the sampling data, in terms of relative quality and intent for use, issued prior to data collection, which helps to ensure that the data collected will be appropriate for the intended objectives of the study
- Were key site characteristics documented? (HHEM - 4.3, 4.5)
  - -- soil/sediment parameters (e.g., particle size, redox potential, mineral class, organic carbon and clay content, bulk density, and porosity)
  - -- hydrogeological parameters (e.g., hydraulic gradient, pH/Eh, hydraulic conductivity, location, saturated thickness, direction, and rate of flow of aquifers, relative location of bedrock layer)

(continued)

EXHIBIT 9-2 (continued)

REVIEWER CHECKLIST

-- hydrological parameters (e.g., hardness, pH, dissolved oxygen, salinity, temperature, total suspended solids, flow rates, and depths of rivers or streams; estuary and embayment parameters such as tidal cycle, range, and area; as well as lake parameters such as area, volume, depth, and depth to thermocline)

-- meteorological parameters (e.g., direction of prevailing wind, average wind speed, temperature, humidity, annual average and 24 hour maximum rainfall)

- Were all appropriate media sampled? (HHEM - 4.4, 4.5, 4.6)

  -- was there adequate justification for any omissions?

  -- were literature estimates employed for omissions in background sampling and were they referenced properly?

- Were all key areas sampled, based on all available information (e.g., preliminary assessment, field screening)? (HHEM - 4.4, 4.5, 4.6)

- Did sampling include media along potential routes of migration (e.g., between the contaminant source and potential future exposure points)? (HHEM - 4.5, 4.6)

- Were sampling locations consistent with nature of contamination (e.g., at the appropriate depth)? (HHEM - 4.5, 4.6)

- Were sampling efforts consistent with field screening and visual observations in locating "hot spots"? (HHEM - 4.5, 4.6)

- Were detailed sampling maps provided, indicating the location, type (e.g., grab, composite, duplicate), and numerical code of each sample? (HHEM - 5.10)

- Did sampling include appropriate QA/QC measures (e.g., replicates, split samples, trip and field blanks)? (HHEM - 4.7, 5.4)

- Were background samples collected from appropriate areas (e.g., areas proximate to the site, free of potential contamination by site chemicals or anthropogenic sources, and similar to the site in topography, geology, meteorology, and other physical characteristics)? (HHEM - 4.4, 5.7)

2.2 Data Evaluation

- Were any site-related chemicals (e.g., human carcinogens) eliminated from analysis without appropriate justification? (HHEM - 5.9)

(continued)

EXHIBIT 9-2 (continued)

REVIEWER CHECKLIST

-- as infrequently detected chemicals (HHEM - 5.3.3, 5.9.3)

-- as non-detects in a specific medium without employing a "proxy" concentration (HHEM - 5.3)

-- as common laboratory contaminants even though sample concentrations were significantly higher than that found in blanks? (HHEM - 5.5)

-- as present at a "ubiquitous level"? (HHEM - 5.7)

- Were inappropriate "proxy concentrations" assigned to site-related chemicals? (HHEM - 5.3)

  -- was a value of zero or the instrument detection limit (IDL) assigned?

  -- was an erroneous sample-specific quantitation limit employed?

- Were appropriate analytical methods employed for collection of data upon which risk estimates are based? (HHEM - 5.2)

  -- were the methods consistent with the requisite level of sensitivity?

  -- were established procedures with adequate QA/QC measures employed?

- Did the data meet the Data Quality Objectives (DQO)? (HHEM - 4.1.4)

  -- were the sampling methods consistent with the intended uses of data?

- Were appropriate data qualifiers employed? (HHEM - 5.4)

- Were special analytical services (SAS) employed when appropriate? (HHEM - 5.3)

  -- was SAS employed as an adjunct to routine analysis in cases where certain contaminants were suspected at low levels, as non-TCL chemicals, in non-standard matrices, or in situations requiring a quick turnaround time?

3.0 CONCERNS IN REVIEWING THE EXPOSURE ASSESSMENT

- Were "reasonable maximum exposures" considered (i.e., the highest exposures that are reasonably expected to occur)? (HHEM - 6.1.2, 6.4.1, 6.6)

- Were current and future land uses considered? (HHEM - 6.1.2, 6.2)

(continued)

EXHIBIT 9-2 (continued)

REVIEWER CHECKLIST

- Was residential land use considered as an alternative future land use? (HHEM - 6.2.2)

  -- if not, was a valid rationale provided?

- Were all potential sensitive subpopulations considered (e.g., elderly people, pregnant or nursing women, infants and children, and people with chronic illnesses)? (HHEM - 6.2.2)

- Were all significant contaminant sources considered? (HHEM - 6.3.1)

- Were all potential contaminant release mechanisms considered, such as volatilization, fugitive dust emission, surface runoff/overland flow, leaching to ground water, tracking by humans/animals, and soil gas generation? (HHEM - 6.3.1)

- Were all potential contaminant transport pathways considered, such as direct air transport downwind, diffusion in surface water, surface water flow, ground-water flow, and soil gas migration? (HHEM - 6.3)

- Were all relevant cross-media transfer effects considered, such as volatilization to air, wet deposition, dry deposition, ground-water discharge to surface, and ground-water recharge from surface water? (HHEM - 6.3)

- Were all media potentially associated with exposure considered? (HHEM - 6.2, 6.3)

- Were all relevant site-specific characteristics considered, including topographical, hydrogeological, hydrological, and meteorological parameters? (HHEM - 6.1, 6.3)

- Were all possible exposure pathways considered? (HHEM - 6.3)

  -- was a valid rationale offered for exclusion of any potential pathways from quantitative evaluation?

- Were all "spatial relationships" adequately considered as factors that could affect the level of exposure (e.g., hot spots in an area that is frequented by children, exposure to ground water from two aquifers that are not hydraulically connected and that differ in the type and extent of contamination)? (HHEM - 6.2, 6.3)

- Were appropriate approaches employed for calculating average exposure concentrations? (HHEM - 6.4, 6.5)

  -- was a valid rationale provided for using geometric or arithmetic means?

- Were appropriate or standard default values used in exposure calculations (e.g., age-specific body weights, appropriate exposure frequency and duration values)? (HHEM - 6.4, 6.5, 6.6)

(continued)

EXHIBIT 9-2 (continued)

REVIEWER CHECKLIST

4.0 CONCERNS IN REVIEWING THE TOXICITY ASSESSMENT

- Was the exclusion of any carcinogen from analysis adequately justified (e.g., were "weight-of-evidence" classifications and completeness of exposure pathways considered in this decision)? (HHEM - 5.9, 7.3)

- Were appropriate "route-to-route" extrapolations performed in cases where a toxicity value was applied across differing routes of exposure? (HHEM - 7.5.1, 8.1.2)

  -- were the extrapolations based on appropriate guidance?

- Were appropriate toxicity values employed based on the nature of exposure? (HHEM - 7.4, 7.5)

  -- were subchronic vs. chronic RfDs applied correctly based on the duration of exposure?

  -- were all sensitive subpopulations, such as pregnant or nursing women potentially requiring developmental RfDs (RfD_{dt}s), considered in the selection of the toxicity values used?

- Were the toxicity values that were used consistent with the values contained within the Integrated Risk Information System (IRIS) or other EPA documents? (HHEM - 7.4, 7.5)

5.0 CONCERNS IN REVIEWING THE RISK CHARACTERIZATION

- Were exposure estimates and toxicity values consistently expressed as either intakes or absorbed doses for each chemical taken through risk characterization? (HHEM - 8.1.2)

  -- was a valid rationale given for employing values based on absorbed dose?

- Were all site-related chemicals that were analyzed in the exposure assessment considered in risk characterization? (HHEM - 8.1.2)

  -- were inconsistencies explained?

- Were risks appropriately summed only across exposure pathways that affect the same individual or population subgroup, and in which the same individual or population subgroup faces the "reasonable maximum exposure," based on the assumptions employed in the exposure assessment? (HHEM - 8.3)

- Were sources of uncertainty adequately characterized? (HHEM - 8.4)

- Were current and future land uses considered?

- Were all significant contaminant sources considered?

- Were appropriate or standard default values used in exposure calculations?

- Were the toxicity values that were used consistent with the values contained within the Integrated Risk Information System (IRIS) or other EPA documents?

Although the checklist addresses many pertinent issues, it is not a complete listing of all potential concerns, since this objective is beyond the scope of a preliminary review tool. In addition, some of the concerns listed are not necessarily appropriate for all risk assessment reports.

The recommended steps in reviewing a risk assessment report are as follows:

(1) compare the risk assessment report outline to the suggested outline in Section 9.1 of this chapter (i.e., Exhibit 9-1);

(2) use the checklist in this section (i.e., Exhibit 9-2); and

(3) conduct a comprehensive review.

The outline (Exhibit 9-1) and the checklist (Exhibit 9-2) are intended only as tools to assist in a preliminary review of a risk assessment, and are not designed to replace the good judgment needed during the comprehensive review. These two tools should provide a framework, however, for the timely screening of risk assessments by reviewers with a moderate level of experience in the area. If these steps are followed in order, then some of the major problems with a risk assessment report (if any) can be identified before significant resources are expended during the comprehensive review.

9.3 MANAGEMENT TOOLS

This section provides a concise checklist for the RPM to use in carrying out their role in the risk assessment process (see Exhibit 9-3). Other decision-makers at the site also may find this checklist useful. Specific points at which the managers should be involved, or may be called upon to become involved, during the risk assessment are discussed in Chapters 4 through 8 of the manual. This checklist extracts information from those chapters, and also includes pointers on planning and involvement for the manager. The purpose of the checklist is to involve managers in the direction and development of the risk assessment and thereby avoid serious mistakes or costly misdirections in focus or level of effort.

Although the checklist is shaped to suggest when and how the manager should become involved in the risk assessment process, it is assumed that part of the manager's involvement will require consultation with technical resources available in the region or state. The checklist advises consulting the "regional risk assessment support staff" at a number of points in the process. This contact may not be one person, but could be a number of different technical people in the region, such as a toxicologist, hydrogeologist, or other technical reviewer. The manager should become aware of the resources available to him or her, and use them when appropriate to ensure that the risk assessment developed is useful and accurate.

EXHIBIT 9-3

CHECKLIST FOR MANAGER INVOLVEMENT

1. GETTING ORGANIZED

   - Ensure that the workplan for the risk assessment contractor support is in place (if needed).
   - Identify EPA risk assessment support personnel (to be used throughout the risk assessment process).
   - Gather relevant information, such as appropriate risk assessment guidances and site-specific data and reports.
   - Identify available state, county, and other non-EPA resources.

2. BEFORE THE SCOPING MEETING

   - Make initial contact with risk assessor.
   - Provide risk assessor with available guidances and site data.
   - Determine (or review) data collection needs for risk assessment, considering:
     -- modeling parameter needs;
     -- type and location of background samples;
     -- the preliminary identification of potential human exposure;
     -- strategies for sample collection appropriate to site/risk assessment data needs;
     -- statistical methods;
     -- QA/QC measures of particular importance to risk assessment;
     -- special analytical services (SAS) needs;
     -- alternate future land use; and
     -- location(s) in ground water that will be used to evaluate future ground-water exposures.

3. AT THE SCOPING MEETING

   - Present risk assessment data collection needs.
   - Ensure that the risk assessment data collection needs will be considered in development of the sampling and analysis plan.
   - Where limited resources require that less-than-optimal sampling be conducted, discuss potential impacts on risk assessment results.

4. AFTER THE SCOPING MEETING

   - Ensure that the risk assessor reviews and approves the sampling and analysis plan.
   - Consult with ATSDR if human monitoring is planned.

(continued)

EXHIBIT 9-3 (continued)

CHECKLIST FOR MANAGER INVOLVEMENT

5. DURING SAMPLING AND ANALYSIS

- Ensure that risk assessment needs are being met during sampling.
- Provide risk assessor with any preliminary sampling results so that he/she can determine if sampling should be refocused.
- Consult with ATSDR to obtain a status report on any human monitoring that is being conducted. Provide any results to risk assessor.

6. DURING DEVELOPMENT OF RISK ASSESSMENT

- Meet with risk assessor to discuss basis of excluding chemicals from the risk assessment (and developing the list of chemicals of potential concern). Confirm appropriateness of excluding chemicals.
- Confirm determination of alternate future land use.
- Confirm location(s) in ground water that will be used to evaluate future ground-water exposures.
- Understand basis for selection of pathways and potentially exposed populations.
- Facilitate discussions between risk assessor and EPA risk assessment support personnel on the following points:
  - -- the need for any major exposure, fate, and transport models (e.g., air or ground-water dispersion models) used;
  - -- site-specific exposure assumptions;
  - -- non-EPA-derived toxicity values; and
  - -- appropriate level of detail for uncertainty analysis, and the degree to which uncertainties will be quantified.
- Discuss and approve combination of pathway risks and hazard indices.
- Ensure that end results of risk characterization have been compared with ATSDR health assessments and other site-specific human studies that might be available.

7. REVIEWING THE RISK ASSESSMENT

- Allow sufficient time for review and incorporation of comments.
- Ensure that reviewers' comments are incorporated.

(continued)

EXHIBIT 9-3 (continued)

CHECKLIST FOR MANAGER INVOLVEMENT

8. COMMUNICATING THE RISK ASSESSMENT

- Plan a briefing among technical staff to discuss significant findings and uncertainties.
- Discuss development of graphics, tools, and presentations to assist risk management decisions.
- Consult with other groups (e.g., community relations staff), as appropriate.
- Brief upper management.

REFERENCES FOR CHAPTER 9

Bean, M.C. (CH2M Hill). 1987. Tools for Environmental Professionals Involved in Risk Communication at Hazardous Waste Facilities Undergoing Siting, Permitting, or Remediation. Presented at the Air Pollution Control Association Annual Meeting. New York. June 21-26, 1987.

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Environmental Protection Agency (EPA). 1988b. Guidance for Conducting Remedial Investigations and Feasibility Studies Under CERCLA. Office of Emergency and Remedial Response. (OSWER Directive 9355.3-01).

Environmental Protection Agency (EPA). 1989. Interim Final Guidance on Preparing Superfund Decision Documents: The Proposed Plan, the Record of Decision, Explanation of Significant Differences, and the Record of Decision Amendment. Office of Emergency and Remedial Response. (OSWER Directive 9355.3-02).

New Jersey Department of Environmental Protection (NJDEP). 1987. Improving Dialogue with Communities: A Short Guide for Government Risk Communication. Division of Science and Research.

CHAPTER 10

RADIATION RISK ASSESSMENT GUIDANCE

There are many sites contaminated with radioactive substances that are included on the National Priorities List (NPL), and additional sites are expected in future NPL updates. This chapter provides supplemental baseline risk assessment guidance for use at these sites. This guidance is intended as an overview of key differences in chemical and radionuclide assessments, and not as a comprehensive, stand-alone approach for assessing the risks posed by radiation.

The reader should be familiar with the guidance provided in Chapters 2 through 9 before proceeding further in Chapter 10. Although the discussions in the previous chapters focus primarily on chemically contaminated sites, much of the information presented is also applicable to the evaluation of radioactively contaminated Superfund sites. For consistency and completeness, the topics discussed in each section of this chapter parallel the topics covered in each of the previous chapters.

After a brief introduction to some of the basic principles and concepts of radiation protection (Section 10.1), seven additional areas are addressed:

(1) Regulation of Radioactively Contaminated Sites (Section 10.2);

(2) Data Collection (Section 10.3);

(3) Data Evaluation (Section 10.4);

(4) Exposure and Dose Assessment (Section 10.5);

ACRONYMS, SYMBOLS, AND UNITS FOR CHAPTER 10

A(t) = Activity at Time t
Bq = Becquerel
Ci = Curie
CLP = Contract Laboratory Program
D = Absorbed Dose
DCF = Dose Conversion Factor Per Unit Intake
H_E = Effective Dose Equivalent
H_T = Dose Equivalent Averaged Over Tissue or Organ T
$H_{E,50}$ = Committed Effective Dose Equivalent Per Unit Intake
$H_{T,50}$ = Committed Dose Equivalent Averaged Over Tissue T
LET = Linear Energy Transfer
LLD = Lower Limit of Detection
MeV = Million Electron Volts
N = Modifying Factor in the Definition of Dose Equivalent
pCi = PicoCurie (10^{-12} Ci)
Q = Quality Factor in Definition of Dose Equivalent
RBE = Relative Biological Effectiveness
SI = International System of Units
Sv = Sievert
T = Tissue or Target Organs
w_T = Weighting Factor in the Definition of Effective Dose Equivalent and Committed Effective Dose Equivalent

(5) Toxicity Assessment (Section 10.6);

(6) Risk Characterization (Section 10.7); and

(7) Documentation, Review, and Management Tools for the Risk Assessor, Reviewer, and Manager (Section 10.8).

DEFINITIONS FOR CHAPTER 10

Absorbed Dose (D). The mean energy imparted by ionizing radiation to matter per unit mass. The special SI unit of absorbed dose is the gray (Gy); the conventional unit is the rad (1 rad = 0.01 Gy).

Becquerel (Bq). One nuclear disintegration per second; the name for the SI unit of activity. 1 Bq = 2.7 x 10^{-11} Ci.

Committed Dose Equivalent ($H_{T,50}$). The total dose equivalent (averaged over tissue T) deposited over the 50-year period following the intake of a radionuclide.

Committed Effective Dose Equivalent ($H_{E,50}$). The weighted sum of committed dose equivalents to specified organs and tissues, in analogy to the effective dose equivalent.

Curie (Ci). 3.7 x 10^{10} nuclear disintegrations per second, the name for the conventional unit of activity. 1 Ci = 3.7 x 10^{10}Bq.

Decay Product(s). A radionuclide or a series of radionuclides formed by the nuclear transformation of another radionuclide which, in this context, is referred to as the parent.

Dose Conversion Factor (DCF). The dose equivalent per unit intake of radionuclide.

Dose Equivalent (H). The product of the absorbed dose (D), the quality factor (Q), and any other modifying factors (N). The SI unit of dose equivalent is the sievert (Sv); the conventional unit is the rem (1 rem = 0.01 Sv).

Effective Dose Equivalent (H_E). The sum over specified tissues of the products of the dose equivalent in a tissue or organ (T) and the weighting factor for that tissue.

External Radiation. Radiations incident upon the body from an external source.

Gray (Gy). The SI unit of absorbed dose. 1Gy = 1 Joule kg^{-1} = 100 rad.

Half-Life (physical, biological, or effective). The time for a quantity of radionuclide, i.e., its activity, to diminish by a factor of a half (because of nuclear decay events, biological elimination of the material, or both.).

Internal Radiation. Radiation emitted from radionuclides distributed within the body.

Ionizing Radiation. Any radiation capable of displacing electrons from atoms or molecules, thereby producing ions.

Linear Energy Transfer (LET). A measure of the rate of energy absorption, defined as the average energy imparted to the absorbing medium by a charged particle per unit distance (KeV per um).

Nuclear Transformation. The spontaneous transformation of one radionuclide into a different nuclide or into a different energy state of the same nuclide.

Quality Factor (Q). The principal modifying factor that is employed in deriving dose equivalent, H, from absorbed dose, D; chosen to account for the relative biological effectiveness (RBE) of the radiation in question, but to be independent of the tissue or organ under consideration, and of the biological endpoint. For radiation protection purposes, the quality factor is determined by the linear energy transfer (LET) of the radiation.

Rad. The conventional unit for absorbed dose of ionizing radiation; the corresponding SI unit is the gray (Gy); 1 rad = 0.01 Gy = 0.01 Joule/kg.

Rem. An acronym of radiation equivalent man, the conventional unit of dose equivalent; the corresponding SI unit is the Sievert; 1 Sv = 100 rem.

Sievert (Sv). The special name for the SI unit of dose equivalent. 1 Sv = 100 rem.

Slope Factor. The age-averaged lifetime excess cancer incidence rate per unit intake (or unit exposure for external exposure pathways) of a radionuclide.

Weighting Factor (w_T). Factor indicating the relative risk of cancer induction or hereditary defects from irradiation of a given tissue or organ; used in calculation of effective dose equivalent and committed effective dose equivalent.

There are special hazards associated with handling radioactive waste and EPA strongly recommends that a health physicist experienced in radiation measurement and protection be consulted prior to initiating any activities at a site suspected of being contaminated with radioactive substances. EPA also recommends that the remedial project manager (RPM) or on-scene coordinator (OSC) should designate both a chemical risk assessor and a radiation risk assessor. These individuals should work closely with each other and the RPM to coordinate remedial activities (e.g., site scoping, health and safety planning, sampling and analysis) and exchange information common to both chemical and radionuclide assessments, including data on the physical characteristics of the site, potentially impacted populations, pathways of concern, and fate and transport models used. At the conclusion of the remedial investigation/feasibility study (RI/FS) process, the RPM should issue a single report that summarizes and integrates the results from both the chemical and the radiation risk assessments.

A two-phase evaluation is described for the radiation risk assessment. As discussed in Section 10.5, procedures established by the International Commission on Radiological Protection (ICRP 1979) and adopted by EPA in *Federal Guidance Report No. 11* (EPA 1988) are used to estimate the radiation dose equivalent to humans from potential exposures to radionuclides through all pertinent exposure pathways at a site. Those estimates of dose equivalent may be used for comparison with established radiation protection standards and criteria. However, this methodology was developed for regulation of occupational radiation exposures for adults and is not completely applicable for estimating health risk to the general population at a Superfund site. Therefore, a separate methodology is presented in Section 10.7.2 for estimating health risk, based on the age-averaged lifetime excess cancer incidence per unit intake (and per unit external exposure) for radionuclides of concern. Radiation risk assessments for Superfund sites should include estimates of both the dose equivalent computed as described in Section 10.5, and the health risk attributable to radionuclide exposures computed using the approach described in Section 10.7.

Only summary-level information is presented in this chapter, and references are provided to a number of supporting technical documents for further information. In particular, the reader is encouraged to consult Volume 1 of the *Background Information Document for the Draft Environmental Impact Statement for Proposed NESHAPS for Radionuclides* (EPA 1989a) for a more comprehensive discussion of EPA's current risk assessment methodology for radionuclides.

For additional radiation risk assessment information and guidance, RPMs and other interested individuals can contact the Office of Radiation Programs (ORP) within EPA headquarters at 202-475-9630 (FTS 475-9630). Interested individuals also can contact the Regional Radiation Program Managers within each of the EPA regional offices for guidance and health physics support.

10.1 RADIATION PROTECTION PRINCIPLES AND CONCEPTS

Radioactive atoms undergo spontaneous nuclear transformations and release excess energy in the form of ionizing radiation. Such transformations are referred to as radioactive decay. As a result of the radioactive decay process, one element is transformed into another; the newly formed element, called a decay product, will possess physical and chemical properties different from those of its parent, and may also be radioactive. A radioactive species of a particular element is referred to as a radionuclide or radioisotope. The exact mode of radioactive transformation for a particular radionuclide depends solely upon its nuclear characteristics, and is independent of the nuclide's chemical characteristics or physical state. A fundamental and unique characteristic of each radionuclide is its radioactive half-life, defined as the time required for one half of the atoms in a given quantity of the radionuclide to decay. Over 1,600 different radionuclides have been identified to date, with half-lives ranging from fractions of a second to millions of years. Selected radionuclides of potential importance at Superfund sites are listed in Exhibit 10-1.

Radiation emitted by radioactive substances can transfer sufficient localized energy to atoms to remove electrons from the electric field of their nucleus (ionization). In living tissue this energy transfer can destroy cellular constituents and produce electrically charged molecules (i.e., free radicals). Extensive biological damage can lead to adverse health effects. The type of ionizing radiation emitted by a particular radionuclide depends upon the exact nature of the nuclear transformation, and may include emission of alpha particles, electrons (beta particles or positrons), and neutrons; each of these transformations may be accompanied by emission of photons (gamma radiation or x-rays). Each type of radiation differs in its physical characteristics and in its ability to inflict damage to biological tissue. These characteristics and effects are summarized in the box on this page.

Quantities of radionuclides are typically expressed in terms of activity at a given time t (A(t)). The SI unit of activity is the becquerel (Bq), which is defined as the quantity of a given radionuclide in which one atom is transformed per second (i.e., one decay per second). The conventional unit of activity is the curie (Ci), which is defined as the quantity of a given radionuclide in which 3.7×10^{10} atoms undergo nuclear transformation each second; one curie is approximately equivalent to the decay rate of one gram of Ra-226. A more convenient unit of activity for expressing environmental concentrations of radionuclides is the picoCurie (pCi), which is equal to 10^{-12} Ci. Occasionally, activity is expressed incorrectly in terms of counts per second (cps) or counts per minute (cpm): these refer to the number of transformations per unit time measured by a particular radiation detector and do not represent the true decay rate of the radionuclide. To derive activity values, count rate measurements are multiplied by radioisotope-specific detector calibration factors.

PRINCIPAL TYPES OF IONIZING RADIATION

Alpha particles are doubly charged cations, composed of two protons and two neutrons, which are ejected monoenergetically from the nucleus of an atom when the neutron to proton ratio is too low. Because of their relatively large mass and charge, alpha particles tend to ionize nearby atoms quite readily, expending their energy in short distances. Alpha particles will usually not penetrate an ordinary sheet of paper or the outer layer of skin. Consequently, alpha particles represent a significant hazard only when taken into the body, where their energy is completely absorbed by small volumes of tissues.

Beta particles are electrons ejected at high speeds from the nucleus of an unstable atom when a neutron spontaneously converts to a proton and an electron. Unlike alpha particles, beta particles are not emitted with discrete energies but are ejected from the nucleus over a continuous energy spectrum. Beta particles are smaller than alpha particles, carry a single negative charge, and possess a lower specific ionization potential. Unshielded beta sources can constitute external hazards if the beta radiation is within a few centimeters of exposed skin surfaces and if the beta energy is greater than 70 keV. Beta sources shielded with certain metallic materials may produce bremsstrahlung (low energy x-ray) radiation which may also contribute to the external radiation exposure. Internally, beta particles have a much greater range than alpha particles in tissue. However, because they cause fewer ionizations per unit path length, beta particles deposit much less energy to small volumes of tissue and, consequently, inflict must less damage than alpha particles.

Positrons are identical to beta particles except that they have a positive charge. A positron is emitted from the nucleus of a neutron-deficient atom when a proton spontaneously transforms into a neutron. Alternatively, in cases where positron emission is not energetically possible, the neutron deficiency may be overcome by electron capture, whereby one of the orbital electrons is captured by the nucleus and united with a proton to form a neutron, or by annihilation radiation, whereby the combined mass of a positron and electron is converted into photon energy. The damage inflicted by positrons to small volumes of tissue is similar to that of beta particles.

Gamma radiations are photons emitted from the nucleus of a radioactive atom. X-rays, which are extra-nuclear in origin, are identical in form to gamma rays, but have slightly lower energy ranges. There are three main ways in which x- and gamma rays interact with matter: the photoelectric effect, the Compton effect, and pair production. All three processes yield electrons which then ionize or excite other atoms of the substance. Because of their high penetration ability, x- and gamma radiations are of most concern as external hazards.

Neutrons are emitted during nuclear fission reactions, along with two smaller nuclei, called fission fragments, and beta and gamma radiation. For radionuclides likely to be encountered at Superfund sites, the rate of spontaneous fission is minute and no significant neutron radiation is expected.

EXHIBIT 10-1

RADIOLOGICAL CHARACTERISTICS OF SELECTED RADIONUCLIDES FOUND AT SUPERFUND SITES[a]

Nuclide	Half-life[c]	Average Radiation Energies (MeV/decay)[b] Alpha	Beta, Electron	x, Gamma	
Am-241	4.32×10^{2} y	5.57×10^{0}	5.21×10^{-2}	3.25×10^{-2}	
Am-243	7.38×10^{3} y	5.36×10^{0}	2.17×10^{-2}	5.61×10^{-2}	
Ba-137m	2.55×10^{0} h	--	6.37×10^{-2}	5.98×10^{-1}	
C-14	5.73×10^{3} y	--	4.95×10^{-2}	--	
Ce-144	2.84×10^{2} d	--	9.22×10^{-2}	2.07×10^{-2}	
Cm-243	2.85×10^{1} y	5.89×10^{0}	1.38×10^{-1}	1.35×10^{-1}	
Cm-244	1.81×10^{1} y	5.89×10^{0}	8.59×10^{-3}	1.70×10^{-3}	
Co-60	5.27×10^{0} y	--	9.65×10^{-2}	2.50×10^{0}	
Cr-51	2.77×10^{1} d	--	3.86×10^{-3}	3.26×10^{-2}	
Cs-134	2.06×10^{0} y	--	1.64×10^{-1}	1.55×10^{0}	
Cs-135	2.30×10^{6} y	--	6.73×10^{-2}	--	
Cs-137	3.00×10^{1} y	--	1.87×10^{-1}	--	
Fe-59	4.45×10^{1} d	--	1.17×10^{-1}	1.19×10^{0}	
H-3	1.23×10^{1} y	--	5.68×10^{-3}	--	
I-129	1.57×10^{7} y	--	6.38×10^{-2}	2.46×10^{-2}	
I-131	8.04×10^{0} d	--	1.92×10^{-1}	3.81×10^{-1}	
K-40	1.28×10^{9} y	--	5.23×10^{-1}	1.56×10^{-1}	
Mn-54	3.13×10^{2} d	--	4.22×10^{-3}	8.36×10^{-1}	
Mo-99	6.60×10^{1} h	--	3.93×10^{-1}	1.50×10^{-1}	
Nb-94	2.03×10^{4} y	--	1.68×10^{-1}	1.57×10^{0}	
Np-237	2.14×10^{6} y	4.85×10^{0}	7.01×10^{-2}	3.46×10^{-2}	
P-32	1.43×10^{1} d	--	6.95×10^{-1}	--	
Pb-210	2.23×10^{1} y	--	3.80×10^{-2}	4.81×10^{-3}	
Po-210	1.38×10^{2} d	5.40×10^{0}	8.19×10^{-8}	8.51×10^{-6}	
Pu-238	8.77×10^{1} y	5.59×10^{0}	1.06×10^{-2}	1.81×10^{-3}	
Pu-239	2.41×10^{4} y	5.24×10^{0}	6.74×10^{-3}	8.07×10^{-4}	
Pu-240	6.54×10^{3} y	5.24×10^{0}	1.06×10^{-2}	1.73×10^{-3}	
Pu-241	1.44×10^{1} y	1.22×10^{-4}	5.25×10^{-3}	2.55×10^{-6}	
Pu-242	3.76×10^{5} y	4.97×10^{0}	8.73×10^{-3}	1.44×10^{-3}	
Ra-226	1.60×10^{3} y	4.86×10^{0}	3.59×10^{-3}	6.75×10^{-3}	
Ra-228	5.75×10^{0} y	--	1.69×10^{-2}	4.14×10^{-9}	
Ru-106	3.68×10^{2} d	--	1.00×10^{-2}	--	
S-35	8.74×10^{1} d	--	4.88×10^{-2}	--	
Sr-89	5.05×10^{1} d	--	5.83×10^{-1}	8.45×10^{-5}	
Sr-90	2.91×10^{1} y	--	1.96×10^{-1}	--	
Tc-99	2.13×10^{5} y	--	1.01×10^{-1}	--	
Tc-99m	6.02×10^{0} h	--	1.62×10^{-2}	1.26×10^{-1}	
Th-230	7.70×10^{4} y	4.75×10^{0}	1.42×10^{-2}	1.55×10^{-3}	
Th-232	1.41×10^{10} y	4.07×10^{0}	1.25×10^{-2}	1.33×10^{-3}	
U-234	2.44×10^{5} y	4.84×10^{0}	1.32×10^{-2}	1.73×10^{-3}	
U-235	7.04×10^{8} y	4.47×10^{0}	4.92×10^{-2}	1.56×10^{-1}	
U-238	4.47×10^{9} y	4.26×10^{0}	1.00×10^{-2}	1.36×10^{-3}	

[a] Source: ICRP 1983 (except Ba-137m data from Kocher 1981).
[b] Computed as the sum of the products of the energies and yields of individual radiations.
[c] Half-life expressed in years (y), days (d), and hours (h).

The activity per unit mass of a given radionuclide is called the specific activity, and is usually expressed in units of becquerels per gram (Bq/g) or curies per gram (Ci/g). The shorter the half-life of the radionuclide, the greater is its specific activity. For example, Co-60 has a radioactive half-life of about 5 years and a specific activity of $4x10^{13}$ Bq/g, whereas Np-237 has a half-life of 2 million years and a specific activity of $3x10^{7}$ Bq/g.

Several terms are used by health physicists to describe the physical interactions of different types of radiations with biological tissue, and to define the effects of these interactions on human health. One of the first terms developed was radiation exposure, which refers to the transfer of energy from a radiation field of x- or gamma rays to a unit mass of air. The unit for this definition of exposure is the roentgen (R), expressed as coulombs of charge per kilogram of air (1 R = $2.58x10^{-4}$ C/kg).

The term exposure is also defined as the physical contact of the human body with radiation. Internal exposure refers to an exposure that occurs when human tissues are subjected to radiations from radionuclides that have entered the body via inhalation, ingestion, injection, or other routes. External exposure refers to the irradiation of human tissues by radiations emitted by radionuclides located outside the body either dispersed in the air or water, on skin surfaces, or deposited on ground surfaces. All types of radiation may contribute to internal exposure, whereas only photon, beta, and neutron radiations contribute significantly to external exposure.

Ionizing radiation can cause deleterious effects on biological tissues only when the energy released during radioactive decay is absorbed in tissue. The absorbed dose (D) is defined as the mean energy imparted by ionizing radiation per unit mass of tissue. The SI unit of absorbed dose is the joule per kilogram, also assigned the special name the gray (1 Gy = 1 joule/kg). The conventional unit of absorbed dose is the rad (1 rad = 100 ergs per gram = 0.01 Gy).

For radiation protection purposes, it is desirable to compare doses of different types of radiation. The absorbed dose of any radiation divided by the absorbed dose of a reference radiation (traditionally 250 kVp x-rays) that produces the same biological endpoint is called the Relative Biological Effectiveness or RBE. For regulatory purposes, an arbitrary consensus RBE estimate called the Quality Factor or Q is often used. The dose equivalent (H) was developed to normalize the unequal biological effects produced from equal absorbed doses of different types of radiation. The dose equivalent is defined as:

$$H = DQN$$

where D is the absorbed dose, Q is a quality factor that accounts for the RBE of the type of radiation emitted, and N is the product of any additional modifying factors. Quality factors currently assigned by the International Commission on Radiological Protection (ICRP) include values of Q=20 for alpha particles, Q=10 for neutrons and protons, and Q=1 for beta particles, positrons, x-rays, and gamma rays (ICRP 1984). These factors may be interpreted as follows: on average, if an equal amount of energy is absorbed, an alpha particle will inflict approximately 20 times more damage to biological tissue than a beta particle or gamma ray, and twice as much damage as a neutron. The modifying factor is currently assigned a value of unity (N=1) for all radiations. The SI unit of dose equivalent is the sievert (Sv), and the conventional unit is the rem (1 rem = 0.01 Sv).

GENERAL HEALTH PHYSICS REFERENCES

Introduction to Health Physics (Cember 1983)

Atoms, Radiation, and Radiation Protection (Turner 1986)

Environmental Radioactivity (Eisenbud 1987)

The Health Physics and Radiological Health Handbook (Shleien and Terpilak 1984)

EFFECTIVE DOSE EQUIVALENT

The effective dose equivalent, H_E , is a weighted sum of dose equivalents to all organs and tissues (ICRP 1977, ICRP 1979), defined as:

$$H_E = \sum_T w_T H_T$$

where w_T is the weighting factor for organ or tissue T and H_T is the mean dose equivalent to organ or tissue T. The factor w_T, which is normalized so that the summation of all the organ weighting factors is equal to one, corresponds to the fractional contribution of organ or tissue T to the total risk of stochastic health effects when the body is uniformly irradiated. Similarly, the committed effective dose equivalent, $H_{E,50}$, is defined as the weighted sum of committed dose equivalents to all irradiated organs and tissues, as follows:

$$H_{E,50} = \sum_T w_T H_{T,50}$$

H_E and $H_{E,50}$ thus reflect both the distribution of dose among the various organs and tissues of the body and their assumed relative sensitivities to stochastic effects. The organ and tissue weighting factor values w_T are as follows: Gonads, 0.25; Breast, 0.15; Red Marrow, 0.12; Lungs, 0.12; Thyroid, 0.03; Bone Surface, 0.03; and Remainder, 0.30 (i.e., a value of $w_T = 0.06$ is applicable to each of the five remaining organs or tissues receiving the highest doses).

The dose delivered to tissues from radiations external to the body occurs only while the radiation field is present. However, the dose delivered to body tissues due to radiations from systemically incorporated radionuclides may continue long after intake of the nuclide has ceased. Therefore, internal doses to specific tissues and organs are typically reported in terms of the committed dose equivalent ($H_{T,50}$), which is defined as the integral of the dose equivalent in a particular tissue T for 50 years after intake (corresponding to a working lifetime).

When subjected to equal doses of radiation, organs and tissues in the human body will exhibit different cancer induction rates. To account for these differences and to normalize radiation doses and effects on a whole body basis for regulation of occupational exposure, the ICRP developed the concept of the effective dose equivalent (H_E) and committed effective dose equivalent ($H_{E,50}$), which are defined as weighted sums of the organ-specific dose equivalents (i.e., $\Sigma\ w_T H_T$) and organ-specific committed dose equivalents (i.e., $\Sigma w_T H_{T,50}$), respectively. Weighting factors, w_T, are based on selected stochastic risk factors specified by the ICRP and are used to average organ-specific dose equivalents (ICRP 1977, 1979). The effective dose equivalent is equal to that dose equivalent, delivered at a uniform whole-body rate, that corresponds to the same number (but possibly a dissimilar distribution) of fatal stochastic health effects as the particular combination of committed organ dose equivalents (see the box on this page).

A special unit, the working level (WL), is used to describe exposure to the short-lived radioactive decay products of radon (Rn-222). Radon is a naturally occurring radionuclide that is of particular concern because it is ubiquitous, it is very mobile in the environment, and it decays through a series of short-lived decay products that can deliver a significant dose to the lung when inhaled. The WL is defined as any combination of short-lived radon decay products in one liter of air that will result in the ultimate emission of 1.3×10^5 MeV of alpha energy. The working level month (WLM) is defined as the exposure to 1 WL for 170 hours (1 working month).

Radiation protection philosophy encourages the reduction of all radiation exposures as low as reasonably achievable (ALARA), in consideration of technical, economic, and social factors. Further, no practice involving radiation exposure should be adopted unless it provides a positive net benefit. In addition to these general guidelines, specific upper limits on radiation exposures and doses have been established by regulatory authorities as described in the following section.

Additional discussion on the measurement of radioactivity is provided in Sections 10.3 and 10.4, and the evaluation of radiation exposure and dose is discussed further in Section 10.5. Discussion of potential health impacts from ionizing radiation is presented in Section 10.6.

10.2 REGULATION OF RADIOACTIVELY CONTAMINATED SITES

Chapter 2 briefly describes the statutes, regulations, guidance, and studies related to the human health evaluation process for chemical contaminants. The discussion describes CERCLA, as amended by SARA, and the RI/FS process. Since radionuclides are classified as hazardous substances under CERCLA, this information is also applicable to radioactively contaminated sites. Chapter 2 also introduces the concept of compliance with applicable or relevant and appropriate requirements (ARARs) in federal and state environmental laws as required by SARA. Guidance on potential ARARs for the remediation of radioactively contaminated sites under CERCLA is available in the *CERCLA Compliance with Other Laws Manual* (EPA 1989c). Only a brief summary of regulatory authorities is presented here.

The primary agencies with regulatory authority for the cleanup of radioactively contaminated sites include EPA, the Nuclear Regulatory Commission (NRC), the Department of Energy (DOE), and state agencies. Other federal agencies, including the Department of Transportation (DOT) and Department of Defense (DOD), also have regulatory programs (but more limited) for radioactive materials. Also, national and international scientific advisory organizations provide recommendations related to radiation protection and radioactive waste management, but have no regulatory authority. The following is a brief description of the main functions and areas of jurisdiction of these agencies and organizations.

- EPA's authority to protect public health and the environment from adverse effects of radiation exposure is derived from several statutes, including the Atomic Energy Act, the Clean Air Act, the Uranium Mill Tailings Radiation Control Act (UMTRCA), the Nuclear Waste Policy Act, the Resource Conservation and Recovery Act (RCRA), and CERCLA. EPA's major responsibilities with regard to radiation include the development of federal guidance and standards, assessment of new technologies, and surveillance of radiation in the environment. EPA also has lead responsibility in the federal government for advising all federal agencies on radiation standards. EPA's radiation standards apply to many different types of activities involving all types of radioactive material (i.e., source, byproduct, special nuclear, and naturally occurring and accelerator produced radioactive material [NARM]). For some of the EPA standards, implementation and enforcement responsibilities are vested in other agencies, such as NRC and DOE.

- NRC licenses the possession and use of certain types of radioactive material at certain types of facilities. Specifically, the NRC is authorized to license source, byproduct, and special nuclear material. The NRC is not authorized to license NARM, although NARM may be partially subject to NRC regulation when it is associated with material licensed by the NRC. Most of DOE's operations are exempt from NRC's licensing and regulatory requirements, as are certain DOD activities involving nuclear weapons and the use of nuclear reactors for military purposes.

- DOE is responsible for conducting or overseeing radioactive material operations at numerous government-owned/contractor-operated facilities. DOE is also responsible for managing several inactive sites that contain radioactive waste, such as sites associated with the Formerly Utilized Sites Remedial Action Program (FUSRAP), the Uranium Mill Tailings Remedial Action Program (UMTRAP), the Grand Junction Remedial

MAJOR FEDERAL LAWS FOR RADIATION PROTECTION

- Atomic Energy Act of 1954, Public Law 83-703 - established the Atomic Energy Commission as the basic regulatory authority for ionizing radiation.
- Energy Reorganization Act of 1974, Public Law 93-438 - amended the Atomic Energy Act, and established the Nuclear Regulatory Commission to regulate nondefense nuclear activities.
- Marine Protection, Research, and Sanctuaries Act of 1972, Public Law 92-532 - established controls for ocean disposal of radioactive waste.
- Safe Drinking Water Act, Public Law 93-523 - mandated regulation of radionuclides in drinking water.
- Clean Air Act Amendments of 1977, Public Law 95-95 - extended coverage of the Act's provisions to include radionuclides.
- Uranium Mill Tailings Radiation Control Act of 1978, Public Law 96-415 - required stabilization and control of byproduct materials (primarily mill tailings) at licensed commercial uranium and thorium processing sites.
- Low-Level Radioactive Waste Policy Act of 1980, Public Law 96-573 - made states responsible for disposal of LLRW generated within their borders and encouraged formation of inter-state compacts.
- Nuclear Waste Policy Act of 1982, Public Law 97-425 - mandated the development of repositories for the disposal of high-level radioactive waste and spent nuclear fuel.
- Low-Level Radioactive Waste Policy Act Amendments of 1985, Public Law 99-240 - amended LLRWPA requirements and

Action Program (GJRAP), and the Surplus Facilities Management Program (SFMP). DOE is authorized to control all types of radioactive materials at sites within its jurisdiction.

- Other federal agencies with regulatory programs applicable to radioactive waste include DOT and DOD. DOT has issued regulations that set forth packaging, labeling, record keeping, and reporting requirements for the transport of radioactive material (see 49 CFR Parts 171 through 179). Most of DOD's radioactive waste management activities are regulated by NRC and/or EPA. However, DOD has its own program for controlling wastes generated for certain nuclear weapon and reactor operations for military purposes. Other agencies, such as the Federal Emergency Management Agency (FEMA) and the Department of the Interior (DOI), may also play a role in radioactive waste cleanups in certain cases.
- States have their own authority and regulations for managing radioactive material and waste. In addition, 29 states (Agreement States) have entered into agreements with the NRC, whereby the Commission has relinquished to the states its regulatory authority over source, byproduct, and small quantities of special nuclear material. Both Agreement States and Nonagreement States can also regulate NARM. Such state-implemented regulations are potential ARARs.
- The National Council on Radiation Protection and Measurements (NCRP) and the International Commission on Radiological Protection (ICRP) provide recommendations on human radiation protection. The NCRP was chartered by Congress to collect, analyze, develop, and disseminate information and recommendations about radiation protection and measurements. The ICRP's function is basically the same, but on an international level. Although neither the NCRP nor the ICRP have regulatory authority, their recommendations serve as the basis for many of the general (i.e., not

source-specific) regulations on radiation protection developed at state and federal levels.

The standards, advisories, and guidance of these various groups are designed primarily to be consistent with each other, often overlapping in scope and purpose. Nevertheless, there are important differences between agencies and programs in some cases. It is important that these differences be well understood so that when more than one set of standards is potentially applicable to or relevant and appropriate for the same CERCLA site, RPMs will be able to evaluate which standards to follow. In general, determination of an ARAR for a site contaminated with radioactive materials requires consideration of the radioactive constituents present and the functional operations that generated the site, whose regulatory jurisdiction the site falls under, and which regulation is most protective, or if relevant and appropriate, most appropriate given site conditions.

For further information on radiation standards, advisories, and guidance, RPMs should consult the detailed ARARs guidance document (EPA 1989c), as well as EPA's ORP and/or Regional Radiation Program Managers.

10.3 DATA COLLECTION

Data collection needs and procedures for sites contaminated with radioactive substances are very similar to those described in Chapter 4 for chemically contaminated sites. There are, however, some basic differences that simplify data collection for radionuclides, including the relative ease and accuracy with which natural background radiation and radionuclide contaminants can be detected in the environment when compared with chemical contaminants.

The pathways of exposure and the mathematical models used to evaluate the potential health risks associated with radionuclides in the environment are similar to those used for evaluating chemical contaminants. Many of the radionuclides found at Superfund sites behave in the environment like trace metals. Consequently, the types of data needed for a radiation risk assessment are very similar to those required for a chemical contaminant risk assessment. For example, the environmental, land use, and demographic data needed and the procedures used to gather the data required to model fate and effect are virtually identical. The primary differences lie in the procedures used to characterize the radionuclide contaminants. In the sections that follow, emphasis is placed on the procedures used to characterize the radionuclide contaminants and not the environmental setting that affects their fate and effects, since the latter has been thoroughly covered in Chapter 4.

10.3.1 RADIATION DETECTION METHODS

Field and laboratory methods used to identify and quantify concentrations of radionuclides in the environment are, in many cases, more exact, less costly, and more easily implemented than those employed for chemical analyses. Selection of a radiometric method depends upon the number of radionuclides of interest, their activities and types of radiations emitted, as well as on the level of sensitivity required and the sample size available. In some cases, the selection process requires prior knowledge of the nature and extent of radioactive contamination present onsite. See the references provided in the box on page 10-12 for detailed guidance on sample collection and preparation, radiochemical procedures, and radiation counters and measurement techniques. The following discussion provides an overview of a few of the radiation detection techniques and instruments currently used to characterize sites contaminated with radioactive materials.

Field methods utilize instrumental techniques rather than radiochemical procedures to determine in-situ identities and concentrations of radionuclides, contamination profiles, and external beta/gamma exposure rates. Field instruments designed for radiation detection (see Exhibit 10-2) are portable, rugged, and relatively insensitive to wide fluctuations in temperature and humidity. At the same time, they are sensitive enough to discriminate between variable levels of background radiation from naturally occurring radionuclides and excess radiation due to radioactive waste. Because of the harsh conditions in which they are sometimes

EXHIBIT 10-2

TYPES OF FIELD RADIATION DETECTION INSTRUMENTS

Instruments	Range of Counting Rate and Other Characteristics	Typical Uses	Remarks
Beta-Gamma Surface Monitors[a]			
Portable Count Rate Meter (Thin Walled or Thin Window G-M Counter)	0-1,000; 0-10,000; 0-100,000 count/min	Surfaces, hands, clothing	Simple, reliable, battery powered
Alpha Surface Monitors			
Portable Air Proportional Counter with Probe	0-100,000 count/min over 100 cm^2	Surfaces, hands, clothing	Not accurate in high humidity; battery powered; fragile window
Portable Gas Flow Counter with Probe	0-100,000 count/min over 100 cm^2	Surfaces, hands, clothing	Not affected by the humidity; battery powered; fragile window
Portable Scintillation Counter with Probe	0-100,000 count/min over 100 cm^2	Surfaces, hands, clothing	Not affected by the humidity; battery powered; fragile window
Air Monitors			
Particle Samplers			
Filter Paper (High-volume)	40 ft^3/min (1.1 m^3/min)	For quick grab samples	Used intermittently; requires separate counter
Filter Paper (Low-volume)	0.1 to 10 ft^3/min (0.003-0.3 m^3/min)	For continuous room air breathing zone monitoring	Used continuously; requires separate counter
Electrostatic Precipitator	3 ft^3/min (0.09 m^3/min)	For continuous monitoring	Sample deposited on cyclindrical shell; requires separate counter
Impinger	20 to 40 ft^3/min (0.6-1.1 m^3/min)	Alpha contamination	Special uses; requires separate counter
Tritium Monitors			
Flow ionization chambers	0.10 pCi/ m^3/min	Continuous monitoring	May be sensitive to other sources of ionization

[a] None of these surface monitors is suitable for tritium detection.

Source: NCRP Report No. 57 (NCRP 1978).

RADIONUCLIDE MEASUREMENT PROCEDURES

Environmental Radiation Measurements (NCRP 1976)

Instrumentation and Monitoring Methods for Radiation Protection (NCRP 1978)

Radiochemical Analytical Procedures for Analysis of Environmental Samples (EPA 1979a)

Eastern Environmental Radiation Facility Radiochemistry Procedures Manual (EPA 1984a)

A Handbook of Radioactivity Measurement Procedures (NCRP 1985a)

operated, and because their detection efficiency varies with photon energy, all field instruments should be properly calibrated in the laboratory against National Bureau of Standards (NBS) radionuclide sources prior to use in the field. Detector response should also be tested periodically in the field against NBS check-sources of known activity.

Commonly used gamma-ray survey meters include Geiger-Muller (G-M) probes, sodium iodide (NaI(Tl)) crystals, and solid-state germanium diodes (Ge(Li)) coupled to ratemeters, scalers, or multichannel analyzers (MCAs). These instruments provide measurements of overall exposure rates in counts per minute, or microRoentgens or microrem per hour. However, only NaI and Ge(Li) detectors with MCAs provide energy spectra of the gamma rays detected and can therefore verify the identity of specific radionuclides. Thin window G-M detectors and Pancake (ionization) probes are used to detect beta particles. Alpha-particle surface monitors include portable air proportional, gas proportional, and zinc sulfide (ZnS) scintillation detectors, which all have very thin and fragile windows. The references in the box on this page provide additional information on several other survey techniques and instruments, such as aerial gamma surveillance used to map gamma exposure rate contours over large areas.

Laboratory methods involve both chemical and instrumental techniques to quantify low-levels of radionuclides in sample media. The preparation of samples prior to counting is an important consideration, especially for samples containing alpha- and beta-emitting radionuclides that either do not emit gamma rays or emit gamma rays of low abundance. Sample preparation is a multistep process that achieves the following three objectives: (1) the destruction of the sample matrix (primarily organic material) to reduce alpha- and beta-particle self-absorption; (2) the separation and concentration of radionuclides of interest to increase resolution and sensitivity; and (3) the preparation of the sample in a suitable form for counting. Appropriate radioactive tracers (i.e., isotopes of the radionuclides of interest that are not present in the sample initially, but are added to the sample to serve as yield determinants) must be selected and added to the sample before a radiochemical procedure is initiated.

For alpha counting, samples are prepared as thin-layer (low mass) sources on membrane filters by coprecipitation with stable carriers or on metal discs by electrodeposition. These sample filters and discs are then loaded into gas proportional counters, scintillation detectors, or alpha spectrometry systems for measurement (see Exhibit 10-3). In a proportional counter, the sample is immersed in a counting gas, usually methane and argon, and subjected to a high voltage field: alpha emissions dissociate the counting gas creating an ionization current proportional to the source strength, which is then measured by the system electronics. In a scintillation detector, the sample is placed in contact with a ZnS phosphor against the window of a photomultiplier (PM) tube: alpha particles induce flashes of light in the phosphor that are converted to an electrical current in the PM tube and measured. Using alpha spectrometry, the sample is placed in a holder in an evacuated chamber facing a solid-state, surface-barrier detector: alpha particles strike the detector and cause electrical impulses, which are sorted by strength into electronic bins and counted. All three systems yield results in counts per minute, which are then converted into activity units using detector- and radionuclide-specific calibration

EXHIBIT 10-3

TYPES OF LABORATORY RADIATION DETECTION INSTRUMENTS [a]

Type of Instrument	Typical Activity Range (mCi)	Typical Sample Form	Data Acquisition and Display
Gas Proportional Counters	10^{-7} to 10^{-3}	Film disc mount, gas	Ratemeter or scaler
Liquid-Scintillation Counters	10^{-7} to 10^{-3}	Up to 20 ml of liquid gel	Accessories for background subtraction, quench correction, internal standard, sample comparison
NaI (T1) Cylindrical or Well Crystals	10^{-6} to 10^{-3}	Liquid, solid, or contained gas, < 4 ml	Ratemeter
			Discriminators for measuring various energy regions
			Multichannel analyzer, or computer plus analog-to-digital converter
			Computational accessories for full-energy-peak identification, quantification, and spectrum stripping
Ionization Chambers	10^{-2} to 10^{3}	Liquid, solid, or contained gas, (can be large in size)	Ionization-current measurement; digital (mCi) readout, as in dose calibrators
Solid-state Detectors	10^{-2} to 10	Various	Multichannel analyzer or computer with various readout options

[a] Source: NCRP Report No. 58 (NCRP 1985a).

values. Alpha spectrometry is the only system, however, that can be used to identify specific alpha-emitting radionuclides.

For beta counting, samples are prepared both as thin-sources and as solutions mixed with scintillation fluid, similar in function to a phosphor. Beta-emitting sources are counted in gas proportional counters at higher voltages than those applied for alpha counting or in scintillation detectors using phosphors specifically constructed for beta-particle detection. Beta-emitters mixed with scintillation fluid are counted in 20 ml vials in beta-scintillation counters: beta-particle interactions with the fluid produce detectable light flashes. Like alpha detectors, beta detectors provide measurements in counts per minute, which are converted to activity units using calibration factors. It should be noted, however, that few detection systems are available for determining the identity of individual beta-emitting radionuclides, because beta particles are emitted as a continuous spectrum of energy that is difficult to characterize and ascribe to any specific nuclide.

It is advisable to count all samples intact in a known geometry on a NaI or Ge(Li) detector system prior to radiochemical analysis, because many radionuclides that emit gamma rays in sufficient abundance and energy can be detected and measured by this process. Even complex gamma-ray spectra emitted by multiple radionuclide sources can be resolved using Ge(Li) detectors, MCAs, and software packages, and specific radionuclide concentrations can be determined. If the sample activity is low or if gamma rays are feeble, then more rigorous alpha or beta analyses are advised.

10.3.2 REVIEWING AVAILABLE SITE INFORMATION

In Chapter 4, reference is made to reviewing the site data for chemical contaminants in accordance with Stage 1 of the Data Quality Objectives (DQO) process (see box on Page 4-4). This process also applies to radionuclides. For further guidance on the applicability of DQOs to radioactively contaminated sites, consult EPA's Office of Radiation Programs.

10.3.3 ADDRESSING MODELING PARAMETER NEEDS

Exhibits 4-1 and 4-2 describe the elements of a conceptual model and the types of information that may be obtained during a site sampling investigation. These exhibits apply to radioactively contaminated sites with only minor modifications. For example, additional exposure pathways for direct external exposure from immersion in contaminated air or water or from contaminated ground surfaces may need to be addressed for certain radionuclides; these exposure pathways are discussed further in subsequent sections. In addition, several of the parameters identified in these exhibits are not as important or necessary for radiological surveys. For example, the parameters that are related primarily to the modeling of organic contaminants, such as the lipid content of organisms, are typically not needed for radiological assessments.

10.3.4 DEFINING BACKGROUND RADIATION SAMPLING NEEDS

As is the case with a chemically contaminated site, the background characteristics of a radioactively contaminated site must be defined reliably in order to distinguish natural background radiation and fallout from the onsite sources of radioactive waste. With the possible exception of indoor sources of Rn-222, it is often possible to make these distinctions because the radiation detection equipment and analytical techniques used are very precise and sensitive. At a chemically contaminated site, there can be many potential and difficult-to-pinpoint offsite sources for the contamination found onsite, confounding the interpretation of field measurements. With a radioactively contaminated site, however, this is not usually a problem because sources of radionuclides are, in general, easier to isolate and identify. In fact, some radionuclides are so specifically associated with particular industries that the presence of a certain radioactive contaminant sometimes acts as a "fingerprint" to identify its source. Additional information on the sources of natural background and man-made radiation in the environment may be found in the references listed in the box on the next page.

NATURAL BACKGROUND RADIATION

Tritium in the Environment (NCRP 1979)

Ionizing Radiation: Sources and Effects (UNSCEAR 1982)

Exposure from the Uranium Series with Emphasis on Radon and its Daughters (NCRP 1984b)

Carbon-14 in the Environment (NCRP 1985c)

Environmental Radioactivity (Eisenbud 1987)

Population Exposure to External Natural Radiation Background in the United States (EPA 1987a)

Ionizing Radiation Exposure of the Population of the United States (NCRP 1987a)

Exposure of the Population of the United States and Canada from Natural Background Radiation (NCRP 1987b)

10.3.5 PRELIMINARY IDENTIFICATION OF POTENTIAL EXPOSURE

Identification of environmental media of concern, the types of radionuclides expected at a site, areas of concern (sampling locations), and potential routes of radionuclide transport through the environment is an important part of the radiological risk assessment process. Potential media of concern include soil, ground water, surface water, air, and biota, as discussed in Chapter 4. Additional considerations for radioactively contaminated sites are listed below.

- Usually a very limited number of radionuclides at a site contribute significantly to the risk. During the site scoping meeting, it is appropriate to consult with a health physicist not only to develop a conceptual model of the facility, but also to identify the anticipated critical radionuclides and pathways.

- In addition to the environmental media identified for chemically contaminated sites, radioactively contaminated sites should be examined for the potential presence of external radiation fields. Many radionuclides emit both beta and gamma radiation, which can create significant external exposures.

- There are other components in the environment that may or may not be critical exposure pathways for the public, but that are very useful indicators of the extent and type of contamination at a site. These components include sediment, aquatic plants, and fish, which may concentrate and integrate the radionuclide contaminants that may be (or have been) present in the aquatic environment at a site. Accordingly, though some components of the environment may or may not be important direct routes of exposure to man, they can serve as indicators of contamination.

10.3.6 DEVELOPING A STRATEGY FOR SAMPLE COLLECTION

The discussions in Chapter 4 regarding sample location, size, type, and frequency apply as well to radioactively contaminated sites with the following additions and qualifications. First, the resolution and sensitivity of radioanalytical techniques permit detection in the environment of most radionuclides at levels that are well below those that are considered potentially harmful. Analytical techniques for nonradioactive chemicals are usually not this sensitive.

For radionuclides, continuous monitoring of the site environment is important, in addition to the sampling and monitoring programs described in Chapter 4. Many field devices that measure external gamma radiation, such as continuous radon monitors and high pressure ionization chambers, provide a real time continuous record of radiation exposure levels and radionuclide concentrations. Such devices are useful for determining the temporal variation of radiation levels at a contaminated site and for comparing these results to the variability observed at background locations. Continuous measure-ments

provide an added level of resolution for quantifying and characterizing radiological risk.

Additional factors that affect the frequency of sampling for radionuclides, besides those discussed in Chapter 4, include the half-lives and the decay products of the radionuclides. Radionuclides with short half-lives, such as Fe-59 (half-life = 44.5 days), have to be sampled more frequently because relatively high levels of contamination can be missed between longer sampling intervals. The decay products of the radionuclides must also be considered, because their presence can interfere with the detection of the parent nuclides of interest, and because they also may be important contributors to risks.

10.3.7 QUALITY ASSURANCE AND QUALITY CONTROL (QA/QC) MEASURES

The QA/QC concepts described in Chapter 4 also apply to sampling and analysis programs for radionuclides, although the procedures differ. Guidance regarding sampling and measurement of radionuclides and QA/QC protocols for their analyses are provided in the publications listed in the box on this page.

The QA/QC protocols used for radionuclide analysis were not developed to meet the evidential needs of the Superfund program; however, it is likely that many of the current radiological QA/QC guidance would meet the intent of Superfund requirements. Some areas where radiological QA/QC guidance may not meet the intent of Superfund are listed below.

- The degree of standardization for radiochemical procedures may be less rigorous in the QA/QC protocols than that required for chemical labs under the Contract Laboratory Program (CLP). In radiochemical laboratories, several different techniques may be used to analyze for a specific radionuclide in a given matrix with comparable results. The CLP requires all participating chemical laboratories to use standardized techniques.
- The required number and type of QC blanks are fewer for radionuclide samples. For example, a "trip" blank is not generally used because radionuclide samples are less likely to be contaminated from direct exposure to air than are samples of volatile organics.

Limited guidance is available that specifies field QA/QC procedures (see the box on this page). These and other issues related to QA/QC guidance for radiological analyses are discussed further in the Section 10.4.

RADIONUCLIDE MEASUREMENT QA/QC PROCEDURES

Quality Control for Environmental Measurements Using Gamma-Ray Spectrometry (EPA 1977b)

Quality Assurance Monitoring Programs (Normal Operation) - Effluent Streams and the Environment (NRC 1979)

Upgrading Environmental Radiation Data (EPA 1980)

Handbook of Analytical Quality Control in Radioanalytical Laboratories (EPA 1987b)

QA Procedures for Health Labs Radiochemistry (American Public Health Association 1987)

10.4 DATA EVALUATION

Chapter 5 describes the procedures for organizing and evaluating data collected during a site sampling investigation for use in risk assessment. The ten-step process outlined for chemical data evaluation is generally applicable to the evaluation of radioactive contaminants, although many of the details must be modified to accommodate differences in sampling and analytical methods.

10.4.1 COMBINING DATA FROM AVAILABLE SITE INVESTIGATIONS

All available data for the site should be gathered for evaluation and sorted by environmental medium sampled, analytical methods, and sampling periods. Decisions should be made, using the process described in Section 5.1, to combine, evaluate individually, or eliminate specific data for use in the quantitative risk assessment.

10.4.2 EVALUATING ANALYTICAL METHODS

As with chemical data, radiological data should be grouped according to the types of analyses performed to determine which data are appropriate for use in quantitative risk assessment. Analytical methods for measuring radioactive contaminants differ from those for measuring organic and inorganic chemicals. Standard laboratory procedures for radionuclide analyses are presented in references, such as those listed in the box on page 10-12. Analytical methods include alpha, beta, and gamma spectrometry, liquid scintillation counting, proportional counting, and chemical separation followed by spectrometry, depending on the specific radionuclides of interest.

Laboratory accreditation procedures for the analysis of radionuclides also differ. Radionuclide analyses are not currently conducted as part of the Routine Analytical Services (RAS) under the Superfund CLP. However, these analyses may be included under Special Analytical Services (SAS). The EPA Environmental Radioactivity Intercomparison Program, coordinated by the Nuclear Radiation Assessment Division of the Environmental Monitoring Systems Laboratory in Las Vegas (EMSL-LV), provides quality assurance oversight for participating radiation measurement laboratories (EPA 1989b). Over 300 federal, state, and private laboratories participate in some phase of the program, which includes analyses for a variety of radionuclides in media (e.g., water, air, milk, and food) with activity concentrations that approximate levels that may be encountered in the environment. Similar intercomparison programs for analysis of thermoluminescent dosimeters (TLDs) for external radiation exposure rate measurements are conducted by the DOE Environmental Measurements Laboratory (EML) and the DOE Radiological and Environmental Services Laboratory (RESL).

In both cases, these intercomparison programs are less comprehensive than the CLP in terms of facility requirements other than analysis of performance evaluation samples, such as laboratory space and procedural requirements, instrumentation, training, and quality control. However, until such time as radiation measurements become fully incorporated in the CLP, use of laboratories that successfully participate in these intercomparison studies may be the best available alternative for ensuring high-quality analytical data. Regardless of laboratory accreditation, all analytical results should be carefully scrutinized and not accepted at face value.

As discussed in Chapter 5 for chemical analyses, radioanalytical results that are not specific for a particular radionuclide (e.g., gross alpha, gross beta) may have limited usefulness for quantitative risk assessment. They can be useful as a screening tool, however. External gamma exposure rate data, although thought of as a screening measurement, can be directly applied as input data for a quantitative risk assessment.

10.4.3 EVALUATING QUANTITATION LIMITS

Lower limits of detection (LLDs), or quantitation limits, for standard techniques for most radionuclide analyses are sufficiently low to ensure the detection of nuclides at activity concentrations well below levels of concern. There are exceptions, however: some radionuclides with very low specific activities, long half-lives, and/or low-energy decay emissions (e.g., I-129, C-14) are difficult to detect precisely using standard techniques. To achieve lower LLDs, a laboratory may: (1) use more sensitive measurement techniques and/or chemical extraction procedures; (2) analyze larger sample sizes; or (3) increase the counting time of the sample. A laboratory may also choose to apply all three options to increase detection capabilities. Exhibit 10-4 presents examples of typical LLDs using standard analytical techniques. The same special considerations noted for chemical analyses

EXHIBIT 10-4

EXAMPLES OF LOWER LIMITS OF DETECTION (LLD) FOR SELECTED RADIONUCLIDES USING STANDARD ANALYTICAL METHODS[a]

Isotope	Sample Media[b]	LLD pCi	LLD Bq	Methodology
Co-60	-Water	10	0.4	Gamma Spectrometry
	-Soil (dry wt.)	0.1	0.004	Gamma Spectrometry
	-Biota (wet wt.)[c]	0.1	0.004	Gamma Spectrometry
	-Air[d]	25	0.9	Gamma Spectrometry
Sr-90	-Water	1	0.04	Radiochemistry
Cs-137	-Water	10	0.4	Gamma Spectrometry
		0.3	0.01	Radiochemistry
	-Soil (dry wt.)	1	0.04	Gamma Spectrometry
		0.3	0.01	Radiochemistry
	-Biota (wet wt.)	1	0.04	Gamma Spectrometry
		0.3	0.01	Radiochemistry
	-Air	30	1	Gamma Spectrometry
Pb-210	-Water	0.2	0.007	Radiochemistry
	-Soil (dry wt.)	0.2	0.007	Radiochemistry
	-Biota (wet wt.)	0.2	0.007	Radiochemistry
	-Air	5	0.2	Radiochemistry
Ra-226	-Water	100	4	Gamma Spectrometry
		0.1	0.004	Radiochemistry
		0.1	0.004	Radon Daughter Emanation
	-Soil (dry wt.)	0.1	0.004	Radon Daughter Emanation
	-Biota (wet wt.)	0.1	0.004	Radon Daughter Emanation
	-Air	1	0.04	Alpha Spectrometry
Th-232	-Water	0.02	0.0007	Alpha Spectrometry
	-Soil (dry wt.)	0.2	0.007	Radiochemistry
	-Biota (wet wt.)	0.02	0.0007	Alpha Spectrometry
	-Air	0.3	0.01	Alpha Proportional Counter
U-234	-Water	0.02	0.0007	Alpha Spectrometry
U-235	-Soil (dry wt.)	0.1	0.004	Alpha Spectrometry
U-238	-Biota (wet wt.)	0.01	0.0004	Alpha Spectrometry
	-Air	0.2	0.007	Alpha Spectrometry

(continued)

EXHIBIT 10-4 (continued)

EXAMPLES OF LOWER LIMITS OF DETECTION (LLD)
FOR SELECTED RADIONUCLIDES USING STANDARD ANALYTICAL METHODS[a]

Isotope	Sample Media[b]	LLD pCi	LLD Bq	Methodology
Pu-238	-Water	0.02	0.0007	Alpha Spectrometry
Pu-239	-Soil (dry wt.)	0.1	0.004	Alpha Spectrometry
Pu-240	-Biota (wet wt.)	0.01	0.0004	Alpha Spectrometry
	-Air	0.2	0.007	Alpha Spectrometry

[a] Source: U.S. Environmental Protection Agency Eastern Environmental Radiation Facility (EPA-EERF), Department of Energy Environmental Measurements Laboratory (DOE-EML), and commercial laboratories. Note that LLDs are radionuclide-, media-, sample size-, and laboratory-specific: higher and lower LLDs than those reported above are possible. The risk assessor should request and report the LLDs supplied by the laboratory performing the analyses.

[b] Nominal sample sizes: water (1 liter), soil (1 kg dry wt.), biota (1 kg wet wt.), and air (1 filter sample).

[c] Biota includes vegetation, fish, and meat.

[d] Air refers to a sample of 300 m^3 of air collected on a filter, which is analyzed for the radionuclide of interest.

would also apply for radionuclides that are not detected in any samples from a particular medium, but are suspected to be present at a site. In these cases, three options may be applied: (1) re-analyze the sample using more sensitive methods; (2) use the LLD value as a "proxy" concentration to evaluate the potential risks at the detection limit; or (3) evaluate the possible risk implication of the radionuclide qualitatively. An experienced health physicist should decide which of these three options would be most appropriate.

When multiple radionuclides are present in a sample, various interferences can occur that may reduce the analytical sensitivity for a particular radionuclide. Also, in some areas of high background radioactivity from naturally occurring radionuclides, it may be difficult to differentiate background contributions from incremental site contamination. It may be possible to eliminate such interferences by radiochemical separation or special instrumental techniques.

A sample with activity that is nondetectable should be reported as less than the appropriate sample and radionuclide-specific LLD value. However, particular caution should be exercised when applying this approach to radionuclides that are difficult to measure and possess unusually high detection limits, as discussed previously. In most cases where a potentially important radionuclide contaminant is suspected, but not detected, in a sample, the sample should be reanalyzed using more rigorous radiochemical procedures and more sophisticated detection techniques.

If radionuclide sample data for a site are reported without sample-specific radionuclide quantitation limits, the laboratory conducting the analyses should be contacted to determine the appropriate LLD values for the analytical techniques and sample media.

10.4.4 EVALUATING QUALIFIED AND CODED DATA

Various data qualifiers and codes may be attached to problem data from inorganic and organic chemical analyses conducted under the CLP as shown in Exhibits 5-4 and 5-5. These include laboratory qualifiers assigned by the laboratory conducting the analysis and data validation qualifiers assigned by personnel involved in data validation. These qualifiers pertain to QA/QC problems and generally indicate questions concerning chemical identity, chemical concentration, or both. No corresponding system of qualifiers has been developed for radioanalytical data, although certain of the CLP data qualifiers might be adopted for use in reporting radioanalytical data. The health physicist should define and evaluate any qualifiers attached to data for radionuclide analyses. Based on the discussions in Chapter 5, the references on methods listed above, and professional judgment, the health physicist should eliminate inappropriate data from use in the risk assessment.

10.4.5 COMPARING CONCENTRATIONS DETECTED IN BLANKS WITH CONCENTRATIONS DETECTED IN SAMPLES

The analysis of blank samples (e.g., laboratory or reagent blanks, field blanks, calibration blanks) is an important component of a proper radioanalytical program. Analysis of blanks provides a measure of contamination introduced into a sample during sampling or analysis activities.

The CLP provides guidance for inorganic and organic chemicals that are not common laboratory contaminants. According to this guidance, if a blank contains detectable levels of any uncommon laboratory chemical, site sample results should be considered positive only if the measured concentration in the sample exceeds five times the maximum amount detected in any blank. Samples containing less than five times the blank concentration should be classified as nondetects, and the maximum blank-related concentration should be specified as the quantitation limit for that chemical in the sample. Though they are not considered to be common laboratory contaminants, radionuclides should not be classified as nondetects using the above CLP guidance. Instead, the health physicist should evaluate all active sample preparation and analytical procedures for possible sources of contamination.

10.4.6 EVALUATING TENTATIVELY IDENTIFIED RADIONUCLIDES

Because radionuclides are not included on the Target Compound List (TCL), they may be classified as tentatively identified compounds (TICs) under CLP protocols. In reality, however, radioanalytical techniques are sufficiently sensitive that the identity and quantity of radionuclides of potential concern at a site can be determined with a high degree of confidence. In some cases, spectral or matrix interferences may introduce uncertainties, but these problems usually can be overcome using special radiochemical and/or instrumental methods. In cases where a radionuclide's identity is not sufficiently well-defined by the available data set: (1) further analyses may be performed using more sensitive methods, or (2) the tentatively identified radionuclide may be included in the risk assessment as a contaminant of potential concern with notation of the uncertainty in its identity and concentration.

10.4.7 COMPARING SAMPLES WITH BACKGROUND

It is imperative to select, collect, and analyze an appropriate number of background samples to be able to distinguish between onsite sources of radionuclide contaminants from radionuclides expected normally in the environment. Background measurements of direct radiation and radionuclide concentrations in all media of concern should be determined at sampling locations geologically similar to the site, but beyond the influence of the site. Screening measurements (e.g., gross alpha, beta, and gamma) should be used to determine whether more sensitive radionuclide-specific analyses are warranted. Professional judgment should be used by the health physicist to select appropriate background sampling locations and analytical techniques. The health physicist should also determine which naturally occurring radionuclides (e.g., uranium, radium, or thorium) detected onsite should be eliminated from the quantitative risk assessment. All man-made radionuclides detected in samples collected should, however, be retained for further consideration.

10.4.8 DEVELOPING A SET OF RADIONUCLIDE DATA AND INFORMATION FOR USE IN A RISK ASSESSMENT

The process described in Section 5.8 for selection of chemical data for inclusion in the quantitative risk assessment generally applies for radionuclides as well. One exception is the lack of CLP qualifiers for radionuclides, as discussed previously. Radionuclides of concern should include those that are positively detected in at least one sample in a given medium, at levels significantly above levels detected in blank samples and significantly above local background levels. As discussed previously, the decision to include radionuclides not detected in samples from any medium but suspected at the site based on historical information should be made by a qualified health physicist.

10.4.9 GROUPING RADIONUCLIDES BY CLASS

Grouping radionuclides for consideration in the quantitative risk assessment is generally unnecessary and inappropriate. Radiation dose and resulting health risk is highly dependent on the specific properties of each radionuclide. In some cases, however, it may be acceptable to group different radioisotopes of the same element that have similar radiological characteristics (e.g., Pu-238/239/240, U-235/238) or belong to the same decay series. Such groupings should be determined very selectively and seldom offer any significant advantage.

10.4.10 FURTHER REDUCTION IN THE NUMBER OF RADIONUCLIDES

For sites with a large number of radionuclides detected in samples from one or more media, the risk assessment should focus on a select group of radionuclides that dominate the radiation dose and health risk to the critical receptors. For example, when considering transport through ground water to distant receptors, transit times may be very long; consequently, only radionuclides with long half-lives or radioactive progeny that are formed during transport may be of concern for that exposure pathway. For direct external exposures, high-energy gamma emitters are of principal concern, whereas

alpha-emitters may dominate doses from the inhalation and ingestion pathways. The important radionuclides may differ for each exposure pathway and must be determined on their relative concentrations, half-lives, environmental mobility, and dose conversion factors (see Section 10.5 for discussion of dose conversion factors) for each exposure pathway of interest.

The total activity inventory and individual concentrations of radionuclides at a Superfund site will change with time as some nuclides decay away and others "grow in" as a result of radioactive decay processes. Consequently, it may be important to evaluate different time scales in the risk assessment. For example, at a site where Ra-226 (half-life = 1600 years) is the only contaminant of concern in soil at some initial time, the Pb-210 (half-life = 22.3 years) and Po-210 (half-life = 138 days) progeny will also become dominant contributors to the activity onsite over a period of several hundred years.

10.4.11 SUMMARIZING AND PRESENTING DATA

Presentation of results of the data collection and evaluation process will be generally the same for radionuclides and chemical contaminants. The sample table formats presented in Exhibits 5-6 and 5-7 are equally applicable to radionuclide data, except that direct radiation measurement data should be added, if appropriate for the radionuclides and exposure pathways identified at the site.

10.5 EXPOSURE AND DOSE ASSESSMENT

This section describes a methodology for estimating the radiation dose equivalent to humans from potential exposures to radionuclides through all pertinent exposure pathways at a remedial site. These estimates of dose equivalent may be used for comparison with radiation protection standards and criteria. However, this methodology has been developed for regulation of occupational radiation exposures for adults and is not completely applicable for estimating health risk to the general population. Section 10.7.2, therefore, describes a separate methodology for estimating health risk.

Chapter 6 describes the procedures for conducting an exposure assessment for chemical contaminants as part of the baseline risk assessment for Superfund sites. Though many aspects of the discussion apply to radionuclides, the term "exposure" is used in a fundamentally different way for radionuclides as compared to chemicals. For chemicals, exposure generally refers to the intake (e.g., inhalation, ingestion, dermal exposure) of the toxic chemical, expressed in units of mg/kg-day. These units are convenient because the toxicity values for chemicals are generally expressed in these terms. For example, the toxicity value used to assess carcinogenic effects is the slope factor, expressed in units of risk of lifetime excess cancers per mg/kg-day. As a result, the product of the intake estimate with the slope factor yields the risk of cancer (with proper adjustments made for absorption, if necessary).

Intakes by inhalation, ingestion, and absorption are also potentially important exposure pathways for radionuclides, although radionuclide intake is typically expressed in units of activity (i.e., Bq or Ci) rather than mass. Radionuclides that enter through these internal exposure pathways may become systemically incorporated and emit alpha, beta, or gamma radiation within tissues or organs. Unlike chemical assessments, an exposure assessment for radioactive contaminants can include an explicit estimation of the radiation dose equivalent. As discussed previously in Section 10.1, the dose equivalent is an expression that takes into consideration both the amount of energy deposited in a unit mass of a specific organ or tissue as a result of the radioactive decay of a specific radionuclide, as well as the relative biological effectiveness of the radiations emitted by that nuclide. (Note that the term dose has a different meaning for radionuclides [dose = energy imparted to a unit mass of tissue] than that used in Chapter 6 for chemicals [dose, or absorbed dose = mass penetrating into an organism].)

Unlike chemicals, radionuclides can have deleterious effects on humans without being taken into or brought in contact with the body. This is because high energy beta particles and photons from radionuclides in contaminated air, water, or soil can travel long distances with only minimum attenuation in these media before depositing their energy in human tissues. External radiation exposures can

result from either exposure to radionuclides at the site area or to radionuclides that have been transported from the site to other locations in the environment. Gamma and x-rays are the most penetrating of the emitted radiations, and comprise the primary contribution to the radiation dose from external exposures. Alpha particles are not sufficiently energetic to penetrate the outer layer of skin and do not contribute significantly to the external dose. External exposure to beta particles primarily imparts a dose to the outer layer skin cells, although high-energy beta radiation can penetrate into the human body.

The quantification of the amount of energy deposited in living tissue due to internal and external exposures to radiation is termed radiation dosimetry. The amount of energy deposited in living tissue is of concern because the potential adverse effects of radiation are proportional to energy deposition. The energy deposited in tissues is proportional to the decay rate of a radionuclide, and not its mass. Therefore, radionuclide quantities and concentrations are expressed in units of activity (e.g., Bq or Ci), rather than in units of mass.

Despite the fundamental difference between the way exposures are expressed for radionuclides and chemicals, the approach to exposure assessment presented in Chapter 6 for chemical contaminants largely applies to radionuclide contaminants. Specifically, the three steps of an exposure assessment for chemicals also apply to radionuclides: (1) characterization of the exposure setting; (2) identification of the exposure pathways; and (3) quantification of exposure. However, some of the methods by which these three steps are carried out are different for radionuclides.

10.5.1 CHARACTERIZING THE EXPOSURE SETTING

Initial characterization of the exposure setting for radioactively contaminated sites is virtually identical to that described in Chapter 6. One additional consideration is that, at sites suspected of having radionuclide contamination, a survey should be conducted to determine external radiation fields using any one of a number of field survey instruments (preferably, G-M tubes and NaI(Tl) field detectors) (see Exhibit 10-2). Health and safety plans should be implemented to reduce the possibility of radiation exposures that are in excess of allowable limits.

REFERENCES ON EXPOSURE ASSESSMENT FOR RADIONUCLIDES

Calculation of Annual Doses to Man from Routine Releases of Reactor Effluents (NRC 1977)

Radiological Assessment: A Textbook on Environmental Dose Analysis (Till and Meyer 1983)

Models and Parameters for Environmental Radiological Assessments (Miller 1984)

Radiological Assessment: Predicting the Transport, Bioaccumulation, and Uptake by Man of Radionuclides Released to the Environment (NCRP 1984a)

Background Information Document, Draft EIS for Proposed NESHAPS for Radionuclides, Volume I, Risk Assessment Methodology (EPA 1989a)

Screening Techniques for Determining Compliance with Environmental Standards (NCRP 1989)

10.5.2 IDENTIFYING EXPOSURE PATHWAYS

The identification of exposure pathways for radioactively contaminated sites is very similar to that described in Chapter 6 for chemically contaminated sites, with the following additional guidance.

- In addition to the various ingestion, inhalation, and direct contact pathways described in Chapter 6, external exposure to penetrating radiation should also be considered. Potential external exposure pathways to be considered include immersion in contaminated air, immersion in contaminated water, and radiation

exposure from ground surfaces contaminated with beta- and photon-emitting radionuclides.

- As with nonradioactive chemicals, environmentally dispersed radionuclides are subject to the same chemical processes that may accelerate or retard their transfer rates and may increase or decrease their bioaccumulation potentials. These transformation processes must be taken into consideration during the exposure assessment.

- Radionuclides undergo radioactive decay that, in some respects, is similar to the chemical or biological degradation of organic compounds. Both processes reduce the quantity of the hazardous substance in the environment and produce other substances. (Note, however, that biological and chemical transformations can never alter, i.e., either increase or decrease, the radioactivity of a radionuclide.) Radioactive decay products can also contribute significantly to the radiation exposure and must be considered in the assessment.

- Chapter 6 presents a series of equations (Exhibits 6-11 through 6-19) for quantification of chemical exposures. These equations and suggested default variable values may be used to estimate radionuclide intakes as a first approximation, if the equations are modified by deleting the body weight and averaging time from the denominator. However, depending upon the characteristics of the radionuclides of concern, consideration of radioactive decay and ingrowth of radioactive decay products may be important additions, as well as the external exposure pathways.

- Chapter 6 also refers to a number of computer models that are used to predict the behavior and fate of chemicals in the environment. While those models may be suitable for evaluations of radioactive contaminants in some cases, numerous models have been developed specifically for evaluating the transport of radionuclides in the environment and predicting the doses and risks to exposed individuals. In general, models developed specifically for radiological assessments should be used. Such models include, for example, explicit consideration of radioactive decay and ingrowth of radioactive decay products. (Contact ORP for additional guidance on the fate and transport models recommended by EPA.)

10.5.3 QUANTIFYING EXPOSURE: GENERAL CONSIDERATIONS

One of the primary objectives of an exposure assessment is to make a reasonable estimate of the maximum exposure to individuals and critical population groups. The equation presented in Exhibit 6-9 to calculate intake for chemicals may be considered to be applicable to exposure assessment for radionuclides, except that the body weight and averaging time terms in the denominator should be omitted. However, as discussed previously, exposures to radionuclides include both internal and external exposure pathways. In addition, radiation exposure assessments do not end with the calculation of intake, but take the calculation an additional step in order to estimate radiation dose equivalent.

The radiation dose equivalent to specified organs and the effective dose equivalent due to intakes of radionuclides by inhalation or ingestion are estimated by multiplying the amount of each radionuclide inhaled or ingested times appropriate dose conversion factors (DCFs), which represent the dose equivalent per unit intake. As noted previously, the effective dose equivalent is a weighted sum of the dose equivalents to all irradiated organs and tissues, and represents a measure of the overall detriment. *Federal Guidance Report No. 11* (EPA 1988) provides DCFs for each of over 700 radionuclides for both inhalation and ingestion exposures. It is important to note, however, that these DCFs were developed for regulation of occupational exposures to radiation and may not be appropriate for the general population.

Radionuclide intake by inhalation and ingestion is calculated in the same manner as chemical intake

except that it is not divided by body weight or averaging time. For radionuclides, a reference body weight is already incorporated into the DCFs, and the dose is an expression of energy deposited per gram of tissue.

If intake of a radionuclide is defined for a specific time period (e.g., Bq/year), the dose equivalent will be expressed in corresponding terms (e.g., Sv/year). Because systemically incorporated radionuclides can remain within the body for long periods of time, internal dose is best expressed in terms of the committed effective dose equivalent, which is equal to the effective dose equivalent over the 50-year period following intake.

External exposures may be determined by monitoring and sampling of the radionuclide concentrations in environmental media, direct measurement of radiation fields using portable instrumentation, or by mathematical modeling. Portable survey instruments that have been properly calibrated can display dose rates (e.g., Sv/hr), and dose equivalents can be estimated by multiplying by the duration of exposure to the radiation field. Alternatively, measured or predicted concentrations in environmental media may be multiplied by DCFs, which relate radionuclide concentrations on the ground, in air, or in water to external dose rates (e.g., Sv/hr per Bq/m^2 for ground contamination or Sv/hr per Bq/m^3 for air or water immersion).

The dose equivalents associated with external and internal exposures are expressed in identical units (e.g., Sv), so that contributions from all pathways can be summed to estimate the total effective dose equivalent value and prioritize risk from different sources.

In general, radiation exposure assessments need not consider acute toxicity effects. Acute exposures are of less concern for radionuclides than for chemicals because the quantities of radionuclides required to cause adverse effects from acute exposure are extremely large and such levels are not normally encountered at Superfund sites. Toxic effects from acute radiation exposures are possible when humans are exposed to the radiation from large amounts of radioactive materials released during a major nuclear plant accident, such as Chernobyl, or during above-ground weapons detonations. Consequently, the exposure and risk assessment guidance for radionuclides presented in this chapter is limited to situations causing chronic exposures to low levels of radioactive contaminants.

10.5.4 QUANTIFYING EXPOSURE: DETERMINING EXPOSURE POINT CONCENTRATIONS

The preferred method for estimating the concentration of chemical or radioactive contaminants at those places where members of the public may come into contact with them is by direct measurement. However, this will not be possible in many circumstances and it may be necessary, therefore, to use environmental fate and transport models to predict contaminant concentrations. Such modeling would be necessary, for example: (1) when it is not possible to obtain representative samples for all radionuclides of concern; (2) when the contaminant has not yet reached the potential exposure points; and (3) when the contaminants are below the limits of detection but, if present, can still represent a significant risk to the public.

Numerous fate and transport models have been developed to estimate contaminant concentrations in ground water, soil, air, surface water, sediments, and food chains. Models developed for chemical contaminants, such as those discussed in Chapter 6, may also be applied to radionuclides with allowance for radioactive decay and ingrowth of decay products. There are also a number of models that have been developed specifically for radionuclides. These models are similar to the models used for toxic chemicals but have features that make them convenient to use for radionuclide pathway analysis, such as explicit consideration of radioactive decay and daughter ingrowth. Available models for use in radiation risk assessments range in complexity from a series of hand calculations to major computer codes. For example, NRC Regulatory Guide 1.109 presents a methodology that may be used to manually estimate dose equivalents from a variety of exposure pathways (NRC 1977). Examples of computerized radiological assessment models include the AIRDOS-EPA code and the EPA-PRESTO family of codes, which are used extensively by EPA to estimate exposures and doses to populations following atmospheric releases of radionuclides and releases from a low-level waste

disposal facility, respectively. Guidance on selection and use of the various models can be obtained from the EPA Office of Radiation Programs.

Exhibit 6-10, Example of Table Format for Summarizing Exposure Concentrations, may be used for radionuclide contaminants, except that radionuclide concentrations are expressed in terms of activity per unit mass or volume of the environmental medium (e.g., Bq/kg, Bq/L) rather than mass.

10.5.5 QUANTIFYING EXPOSURE: ESTIMATING INTAKE AND DOSE EQUIVALENT

Section 6.6 presents a description of the methods used to estimate intake rates of contaminants from the various exposure pathways. Exhibits 6-11 to 6-19 present the equations and input assumptions recommended for use in intake calculations. In concept, those equations and assumptions also apply generally to radionuclides, except that the body weight and averaging time terms in the denominators should be omitted. However, as discussed previously, the product of these calculations for radionuclides is an estimate of the radionuclide intake, expressed in units of activity (e.g., Bq), as opposed to mg/kg-day. In addition, the endpoint of a radiation exposure assessment is radiation dose, which is calculated using DCFs as explained below. As explained previously, dose equivalents calculated in the following manner should be used to compare with radiation protection standards and criteria, not to estimate risk.

Internal Exposure. Exhibits 6-11, 6-12, 6-14, 6-17, 6-18, and 6-19 present simplified models for the ingestion of water, food, and soil as pathways for the intake of environmental contaminants. The recommended assumptions for ingestion rates and exposure durations are applicable to radionuclide exposures and may be used to estimate the intake rates of radionuclides by these pathways. As noted previously, however, these intake estimates for radionuclides should not be divided by the body weight or averaging time. These intake rates must be multiplied by appropriate DCF values in order to obtain committed effective dose equivalent values. The more rigorous and complex radionuclide pathway models noted previously typically require much more extensive input data and may include default parameter values that differ somewhat from the values recommended in these exhibits.

Exhibit 6-16 presents the equation and assumptions used to estimate the contaminant intake from air. For radionuclides, the dose from inhalation of contaminated air is determined as the product of the radionuclide concentration in air (Bq/m^3), the breathing rate (m^3 per day or year), exposure duration (day or year), and the inhalation DCF (Sv per Bq inhaled). The result of this calculation is the committed effective dose equivalent, in units of Sv.

Chapter 6 points out that dermal absorption of airborne chemicals is not an important route of uptake. This point is also true for most radionuclides, except airborne tritiated water vapor, which is efficiently taken into the body through dermal absorption. In order to account for this route of uptake, the inhalation DCF for tritium includes an adjustment factor to account for dermal absorption.

External Exposure. Immersion in air containing certain beta-emitting and/or photon-emitting radioactive contaminants can also result in external exposures. Effective dose equivalents from external exposure are calculated as the product of the airborne radionuclide concentration (Bq/m^3), the external DCF for air immersion (Sv/hr per Bq/m^3), and the duration of exposure (hours).

Exhibits 6-13 and 6-15 illustrate the dermal uptake of contaminants resulting from immersion in water or contact with soil. This route of uptake can be important for many organic chemicals; however, dermal uptake is generally not an important route of uptake for radionuclides, which have small dermal permeability constants. External radiation exposure due to submersion in water contaminated with radionuclides is possible and is similar to external exposure due to immersion in air. However, because of the shielding effects of water and the generally short durations of such exposures, immersion in water is typically of lesser significance. The product of the radionuclide concentration in water (Bq/m^3), the relevant DCF (Sv/hr per Bq/m^3), and the duration of exposure (hours) yields effective dose equivalent.

The third external exposure pathway of potential significance is irradiation from radionuclides deposited on the ground surface. Effective dose equivalents resulting from this pathway may be estimated as the product of the soil surface concentration (Bq/m^2) of photon-emitting radionuclides of concern, the external DCF for ground surface exposure (Sv/hr per Bq/m^2), and the duration of exposure (hours).

10.5.6 COMBINING INTAKES AND DOSES ACROSS PATHWAYS

The calculations described previously result in estimates of committed effective dose equivalents (Sv) from individual radionuclides via a large number of possible exposure pathways. Because a given population may be subject to multiple exposure pathways, the results of the exposure assessment should be organized by grouping all applicable exposure pathways for each exposed population. Risks from various exposure pathways and contaminants then can be integrated during the risk characterization step (see Section 10.7).

10.5.7 EVALUATING UNCERTAINTY

The radiation exposure assessment should include a discussion of uncertainty, that, at a minimum, should include: (1) a tabular summary of the values used to estimate exposures and doses and the range of these values; and (2) a summary of the major assumptions of the exposure assessment, including the uncertainty associated with each assumption and how it might affect the exposure and dose estimates. Sources of uncertainty that must be addressed include: (1) how well the monitoring data represent actual site conditions; (2) the exposure models, assumptions, and input variables used to estimate exposure point concentrations; and (3) the values of the variables used to estimate intakes and external exposures. More comprehensive discussions of uncertainty associated with radiological risk assessment are provided in the *Background Information Document for the Draft EIS for Proposed NESHAPS for Radionuclides* (EPA 1989a), *Radiological Assessment* (Till and Meyer 1983), and NCRP Report No. 76 (NCRP 1984a).

10.5.8 SUMMARIZING AND PRESENTING EXPOSURE ASSESSMENT RESULTS

Exhibit 6-22 presents a sample format for summarizing the results of the exposure assessment. The format may also be used for radionuclide contaminants except that the entries should be specified as committed effective dose equivalents (Sv) and the annual estimated intakes (Bq) for each radionuclide of concern. The intakes and dose estimates should be tabulated for each exposure pathway so that the most important radionuclides and pathways contributing to the total health risk may be identified.

The information should be organized by exposure pathway, population exposed, and current and future use assumptions. For radionuclides, however, it may not be necessary to summarize short-term and long-term exposures separately as specified for chemical contaminants.

10.6 TOXICITY ASSESSMENT

Chapter 7 describes the two-step process employed to assess the potential toxicity of a given chemical contaminant. The first step, hazard identification, is used to determine whether exposure to a contaminant can increase the incidence of an adverse health effect. The second step, dose-response assessment, is used to quantitatively evaluate the toxicity information and characterize the relationship between the dose of the contaminant administered or received and the incidence of adverse health effects in the exposed population.

There are certain fundamental differences between radionuclides and chemicals that somewhat simplify toxicity assessment for radionuclides. As discussed in the previous sections, the adverse effects of exposure to radiation are due to the energy deposited in sensitive tissue, which is referred to as the radiation dose. In theory, any dose of radiation has the potential to produce an adverse effect. Accordingly, exposure to any radioactive substances is, by definition, hazardous.

Dose-response assessment for radionuclides is also more straightforward. The type of effects and

the likelihood of occurrence of any one of a number of possible adverse effects from radiation exposure depends on the radiation dose. The relationship between dose and effect is relatively well characterized (at high doses) for most types of radiations. As a result, the toxicity assessment, within the context that it is used in this manual, need not be explicitly addressed in detail for individual radionuclides at each contaminated site.

The sections that follow provide a brief summary of the human and experimental animal studies that establish the hazard and dose-response relationship for radiation exposure. More detailed discussions of radiation toxicity are provided in publications of the National Academy of Sciences Committee on Biological Effects of Ionizing Radiation (BEIR), the United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR), NRC, NCRP, and ICRP listed in the box on this page.

REFERENCES ON HEALTH EFFECTS OF RADIATION EXPOSURE

Recommendations of the ICRP (ICRP 1977)

Limits for Intake of Radionuclides by Workers (ICRP 1979)

Influence of Dose and Its Distribution in Time on Dose-Response Relationships for Low-LET Radiations (NCRP 1980)

The Effects on Populations of Exposure to Low Levels of Ionizing Radiation (NAS 1980)

Induction of Thyroid Cancer by Ionizing Radiation (NCRP 1985b)

Lung Cancer Risk from Indoor Exposures to Radon Daughters (ICRP 1987)

Health Risks of Radon and Other Internally Deposited Alpha-Emitters (National Academy of Sciences 1988)

Ionizing Radiation: Sources, Effects, and Risks (UNSCEAR 1988)

Health Effects Models for Nuclear Power Plant Accident Consequence Analysis: Low-LET Radiation (NRC 1989)

10.6.1 HAZARD IDENTIFICATION

The principal adverse biological effects associated with ionizing radiation exposures from radioactive substances in the environment are carcinogenicity, mutagenicity, and teratogenicity. Carcinogenicity is the ability to produce cancer. Mutagenicity is the property of being able to induce genetic mutation, which may be in the nucleus of either somatic (body) or germ (reproductive) cells. Mutations in germ cells lead to genetic or inherited defects. Teratogenicity refers to the ability of an agent to induce or increase the incidence of congenital malformations as a result of permanent structural or functional deviations produced during the growth and development of an embryo (more commonly referred to as birth defects). Radiation may induce other deleterious effects at acute doses above about 1 Sv, but doses of this magnitude are not normally associated with radioactive contamination in the environment.

As discussed in Section 10.1, ionizing radiation causes injury by breaking molecules into electrically charged fragments (i.e., free radicals), thereby producing chemical rearrangements that may lead to permanent cellular damage. The degree of biolog--ical damage caused by various types of radiation varies according to how spatially close together the ionizations occur. Some ionizing radiations (e.g., alpha particles) produce high density regions of ionization. For this reason, they are called high-LET (linear energy transfer) particles. Other types of radiation (e.g., x-rays, gamma rays, and beta particles) are called low-LET radiations because of the low density pattern of ionization they produce. In equal doses, the carcinogenicity and mutagenicity of high-LET radiations may be an order of magnitude or more greater than those of low-LET radiations, depending on the endpoint being evaluated. The variability in biological effectiveness is accounted for by the quality factor used to calculate the dose equivalent (see Section 10.1).

Carcinogenesis. An extensive body of literature exists on radiation carcinogenesis in man and animals. This literature has been reviewed most recently by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiations (NAS-BEIR Committee) (UNSCEAR

1977, 1982, 1988; NAS 1972, 1980, 1988). Estimates of the average risk of fatal cancer from low-LET radiation from these studies range from approximately 0.007 to 0.07 fatal cancers per sievert.

An increase in cancer incidence or mortality with increasing radiation dose has been demonstrated for many types of cancer in both human populations and laboratory animals (UNSCEAR 1982, 1988; NAS 1980, 1988). Studies of humans exposed to internal or external sources of ionizing radiation have shown that the incidence of cancer increases with increased radiation exposure. This increased incidence, however, is usually associated with appreciably greater doses and exposure frequencies than those encountered in the environment. Therefore, risk estimates from small doses obtained over long periods of time are determined by extrapolating the effects observed at high, acute doses. Malignant tumors in various organs most often appear long after the radiation exposure, usually 10 to 35 years later (NAS 1980, 1988; UNSCEAR 1982, 1988). Radionuclide metabolism can result in the selective deposition of certain radionuclides in specific organs or tissues, which, in turn, can result in larger radiation doses and higher-than-normal cancer risk in these organs.

Ionizing radiation can be considered pancarcinogenic, i.e., it acts as a complete carcinogen in that it serves as both initiator and promoter, and it can induce cancers in nearly any tissue or organ. Radiation-induced cancers in humans have been reported in the thyroid, female breast, lung, bone marrow (leukemia), stomach, liver, large intestine, brain, salivary glands, bone, esophagus, small intestine, urinary bladder, pancreas, rectum, lymphatic tissues, skin, pharynx, uterus, ovary, mucosa of cranial sinuses, and kidney (UNSCEAR 1977, 1982, 1988; NAS 1972, 1980, 1988). These data are taken primarily from studies of human populations exposed to high levels of radiation, including atomic bomb survivors, underground miners, radium dial painters, patients injected with thorotrast or radium, and patients who received high x-ray doses during various treatment programs. Extrapolation of these data to much lower doses is the major source of uncertainty in determining low-level radiation risks (see EPA 1989a). It is assumed that no lower threshold exists for radiation carcinogenesis.

On average, approximately 50 percent of all of the cancers induced by radiation are lethal. The fraction of fatal cancers is different for each type of cancer, ranging from about 10 percent in the case of thyroid cancer to 100 percent in the case of liver cancer (NAS 1980, 1988). Females have approximately 2 times as many total cancers as fatal cancers following radiation exposure, and males have approximately 1.5 times as many (NAS 1980).

Mutagenesis. Very few quantitative data are available on radiogenic mutations in humans, particularly from low-dose exposures. Some mutations are so mild they are not noticeable, while other mutagenic effects that do occur are similar to nonmutagenic effects and are therefore not necessarily recorded as mutations. The bulk of data supporting the mutagenic character of ionizing radiation comes from extensive studies of experimental animals (UNSCEAR 1977, 1982, 1988; NAS 1972, 1980, 1988). These studies have demonstrated all forms of radiation mutagenesis, including lethal mutations, translocations, inversions, nondisjunction, and point mutations. Mutation rates calculated from these studies are extrapolated to humans and form the basis for estimating the genetic impact of ionizing radiation on humans (NAS 1980, 1988; UNSCEAR 1982, 1988). The vast majority of the demonstrated mutations in human germ cells contribute to both increased mortality and illness (NAS 1980; UNSCEAR 1982). Moreover, the radiation protection community is generally in agreement that the probability of inducing genetic changes increases linearly with dose and that no "threshold" dose is required to initiate heritable damage to germ cells.

The incidence of serious genetic disease due to mutations and chromosome aberrations induced by radiation is referred to as genetic detriment. Serious genetic disease includes inherited ill health, handicaps, or disabilities. Genetic disease may be manifest at birth or may not become evident until some time in adulthood. Radiation-induced genetic detriment includes impairment of life, shortened life span, and increased hospitalization. The frequency of radiation-induced genetic impairment is relatively small in comparison with the magnitude of detriment associated with spontaneously arising genetic diseases (UNSCEAR 1982, 1988).

Teratogenesis. Radiation is a well-known teratogenic agent. The developing fetus is much more sensitive to radiation than the mother. The age of the fetus at the time of exposure is the most important factor in determining the extent and type of damage from radiation. The malformations produced in the embryo depend on which cells, tissues, or organs in the fetus are most actively differentiating at the time of radiation exposure. Embryos are relatively resistant to radiation-induced teratogenic effects during the later stages of their development and are most sensitive from just after implantation until the end of organogenesis (about two weeks to eight weeks after conception) (UNSCEAR 1986; Brent 1980). Effects on nervous system, skeletal system, eyes, genitalia, and skin have been noted (Brent 1980). The brain appears to be most sensitive during development of the neuroblast (these cells eventually become the nerve cells). The greatest risk of brain damage for the human fetus occurs at 8 to 15 weeks, which is the time the nervous system is undergoing the most rapid differentiation and proliferation of cells (Otake 1984).

10.6.2 DOSE-RESPONSE RELATIONSHIPS

This section describes the relationship of the risk of fatal cancer, serious genetic effects, and other detrimental health effects to exposure to low levels of ionizing radiation. Most important from the standpoint of the total societal risk from exposures to low-level ionizing radiation are the risks of cancer and genetic mutations. Consistent with our current understanding of their origins in terms of DNA damage, these effects are believed to be stochastic; that is, the probability (risk) of these effects increases with the dose of radiation, but the severity of the effects is independent of dose. For neither induction of cancer nor genetic effects, moreover, is there any convincing evidence for a "threshold" (i.e., some dose level below which the risk is zero). Hence, so far as is known, any dose of ionizing radiation, no matter how small, might give rise to a cancer or to a genetic effect in future generations. Conversely, there is no way to be certain that a given dose of radiation, no matter how large, has caused an observed cancer in an individual or will cause one in the future.

Exhibit 10-5 summarizes EPA's current estimates of the risk of adverse effects associated with human exposure to ionizing radiation (EPA 1989a). Important points from this summary table are provided below.

- Very large doses (>1 Sv) of radiation are required to induce acute and irreversible adverse effects. It is unlikely that such exposures would occur in the environmental setting associated with a potential Superfund site.

- The risks of serious noncarcinogenic effects associated with chronic exposure to radiation include genetic and teratogenic effects. Radiation-induced genetic effects have not been observed in human populations, and extrapolation from animal data reveals risks per unit exposure that are smaller than, or comparable to, the risk of cancer. In addition, the genetic risks are spread over several generations. The risks per unit exposure of serious teratogenic effects are greater than the risks of cancer. However, there is a possibility of a threshold, and the exposures must occur over a specific period of time during gestation to cause the effect. Teratogenic effects can be induced only during the nine months of pregnancy. Genetic effects are induced during the 30-year reproductive generation and cancer can be induced at any point during the lifetime. If a radiation source is not controlled, therefore, the cumulative risk of cancer may be many times greater than the risk of genetic or teratogenic effects due to the potentially longer period of exposure.

EXHIBIT 10-5

SUMMARY OF EPA'S RADIATION RISK FACTORS[a]

Risk	Significant Exposure Period	Risk Factor Range
Low LET (Gy^{-1})		
Teratogenic:[b]		
Severe mental retardation	Weeks 8 to 15 of gestation	0.25-0.55
Genetic:		
Severe hereditary defects, all generations	30-year reproductive generation	0.006-0.11
Somatic:		
Fatal cancers	Lifetime	0.012-0.12
	In utero	0.029-0.10
All cancers	Lifetime	0.019-0.19
High LET (Gy^{-1})		
Genetic:		
Severe hereditary defects, all generations	30-year reproductive generation	0.016-0.29
Somatic:		
Fatal cancers	Lifetime	0.096-0.96
All cancers	Lifetime	0.15-1.5
Radon Decay Products (10^{-6} WLM^{-1})		
Fatal lung cancer	Lifetime	140-720

[a] In addition to the stochastic risks indicated, acute toxicity may occur at a mean lethal dose of 3-5 Sv with a threshold in excess of 1 Sv.

[b] The range assumes a linear, non-threshold dose-response. However, it is plausible that a threshold may exist for this effect.

Based on these observations, it appears that the risk of cancer is limiting and may be used as the sole basis for assessing the radiation-related human health risks of a site contaminated with radionuclides.

For situations where the risk of cancer induction in a specific target organ is of primary interest, the committed dose equivalent to that organ may be multiplied by an organ-specific risk factor. The relative radiosensitivity of various organs (i.e., the cancer induction rate per unit dose) differs markedly for different organs and varies as a function of the age and sex of the exposed individual. Tabulations of such risk factors as a function of age and sex are provided in the *Background Information Document for the Draft Environmental Impact Statement for Proposed NESHAPS for Radionuclides* (EPA 1989a) for cancer mortality and cancer incidence.

10.7 RISK CHARACTERIZATION

The final step in the risk assessment process is risk characterization. This is an integration step in which the risks from individual radionuclides and pathways are quantified and combined where appropriate. Uncertainties also are examined and discussed in this step.

10.7.1 REVIEWING OUTPUTS FROM THE TOXICITY AND EXPOSURE ASSESSMENTS

The exposure assessment results should be expressed as estimates of radionuclide intakes by inhalation and ingestion, exposure rates and duration for external exposure pathways, and committed effective dose equivalents to individuals from all relevant radionuclides and pathways. The risk assessor should compile the supporting documentation to ensure that it is sufficient to support the analysis and to allow an independent duplication of the results. The review should also confirm that the analysis is reasonably complete in terms of the radionuclides and pathways addressed.

In addition, the review should evaluate the degree to which the assumptions inherent in the analysis apply to the site and conditions being addressed. The mathematical models used to calculate dose use a large number of environmental transfer factors and dose conversion factors that may not always be entirely applicable to the conditions being analyzed. For example, the standard dose conversion factors are based on certain generic assumptions regarding the characteristics of the exposed individual and the chemical and physical properties of the radionuclides. Also, as is the case for chemical contaminants, the environmental transfer factors used in the models may not apply to all settings.

Though the risk assessment models may include a large number of radionuclides and pathways, the important radionuclides and pathways are usually few in number. As a result, it is often feasible to check the computer output using hand calculations. This type of review can be performed by health physicists familiar with the models and their limitations. Guidance on conducting such calculations is provided in numerous references, including Till and Meyer (1983) and NCRP Report No. 76 (NCRP 1984a).

10.7.2 QUANTIFYING RISKS

Given that the results of the exposure assessment are virtually complete, correct, and applicable to the conditions being considered, the next step in the process is to calculate and combine risks. As discussed previously, the risk assessment for radionuclides is somewhat simplified because only radiation carcinogenesis needs to be considered.

Section 10.5 presents a methodology for estimating committed effective dose equivalents that may be compared with radiation protection standards and criteria. Although the product of these dose equivalents (Sv) and an appropriate risk factor (risk per Sv) yields an estimate of risk, the health risk estimate derived in such a manner is not completely applicable for members of the general public. A better estimate of risk may be computed using age- and sex-specific coefficients for individual organs receiving significant radiation doses. This information may be used along with organ-specific dose conversion factors to derive slope factors that represent the age-averaged lifetime excess cancer incidence per unit intake for the radionuclides of concern. The Integrated Risk Information System (IRIS) contains slope factor values for radionuclides of concern at remedial sites for each of the four

major exposure pathways (inhalation, ingestion, air immersion, and ground-surface irradiation), along with supporting documentation for the derivation of these values (see Chapter 7 for more detail on IRIS).

The slope factors from the IRIS data base for the inhalation pathway should be multiplied by the estimated inhaled activity (derived using the methods presented in Section 6.6.3 and Exhibit 6-16, without division of the body weight and averaging time) for each radionuclide of concern to estimate risks from the inhalation pathway. Similarly, risks from the ingestion pathway should be estimated by multiplying the ingestion slope factors by the activity ingested for each radionuclide of concern (derived using the methods presented in Exhibits 6-11, 6-12, 6-14, 6-17, 6-18, and 6-19, without division by the body weight and averaging time). Estimates of the risk from the air immersion pathway should be computed by multiplying the appropriate slope factors by the airborne radionuclide concentration (Bq/m^3) and the duration of exposure. Risk from the ground surface pathway should be computed as the product of the slope factor, the soil concentration (Bq/m^2), and the duration of exposure for each radionuclide of concern.

The sum of the risks from all radionuclides and pathways yields the lifetime risk from the overall exposure. As discussed in Chapter 8, professional judgment must be used in combining the risks from various pathways, as it may not be physically possible for one person to be exposed to the maximum radionuclide concentrations for all pathways.

10.7.3 COMBINING RADIONUCLIDE AND CHEMICAL CANCER RISKS

Estimates of the lifetime risk of cancer to exposed individuals resulting from radiological and chemical risk assessments may be summed in order to determine the overall potential human health hazard associated with a site. Certain precautions should be taken, however, before summing these risks. First, the risk assessor should evaluate whether it is reasonable to assume that the same individual can receive the maximum radiological and chemical dose. It is possible for this to occur in some cases because many of the environmental transport processes and routes of exposure are the same for radionuclides and chemicals.

In cases where different environmental fate and transport models have been used to predict chemical and radionuclide exposure, the mathematical models may incorporate somewhat different assumptions. These differences can result in incompatibilities in the two estimates of risk. One important difference of this nature is how the cancer toxicity values (i.e., slope factors) were developed. For both radionuclides and chemicals, cancer toxicity values are obtained by extrapolation from experimental and epidemiological data. For radionuclides, however, human epidemiological data form the basis of the extrapolation, while for many chemical carcinogens, laboratory experiments are the primary basis for the extrapolation. Another even more fundamental difference between the two is that slope factors for chemical carcinogens generally represent an upper bound or 95th percent confidence limit value, while radionuclide slope factors are best estimate values.

In light of these limitations, the two sets of risk estimates should be tabulated separately in the final baseline risk assessment.

10.7.4 ASSESSING AND PRESENTING UNCERTAINTIES

Uncertainties in the risk assessment must be evaluated and discussed, including uncertainties in the physical setting definition for the site, in the models used, in the exposure parameters, and in the toxicity assessment. Monte Carlo uncertainty analyses are frequently performed as part of the uncertainty and sensitivity analysis for radiological risk assessments. A summary of the use of uncertainty analyses in support of radiological risk assessments is provided in NCRP Report No. 76 (NCRP 1984a), *Radiological Assessment* (Till and Meyer 1983), and in the *Background Information Document for the Draft EIS for Proposed NESHAPs for Radionuclides* (EPA 1989a).

10.7.5 SUMMARIZING AND PRESENTING THE BASELINE RISK CHARACTERIZATION RESULTS

The results of the baseline risk characterization should be summarized and presented in an effective manner to assist in decision-making. The estimates of risk should be summarized in the context of the specific site conditions. Information should include the identity and concentrations of radionuclides, types and magnitudes of health risks predicted, uncertainties in the exposure estimates and toxicity information, and characteristics of the site and potentially exposed populations. A summary table should be provided in a format similar to that shown in Exhibit 6-22, as well as graphical presentations of the predicted health risks (see Exhibit 8-7).

10.8 DOCUMENTATION, REVIEW, AND MANAGEMENT TOOLS FOR THE RISK ASSESSOR, REVIEWER, AND MANAGER

The discussion provided in Chapter 9 also applies to radioactively contaminated sites. The suggested outline provided in Exhibit 9-1 may also be used for radioactively contaminated sites with only minor modifications. For example, the portions that uniquely pertain to the CLP program and noncarcinogenic risks are not needed. In addition, because radionuclide hazard and toxicity have been addressed adequately on a generic basis, there is no need for an extensive discussion of toxicity in the report.

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APPENDIX A

ADJUSTMENTS FOR ABSORPTION EFFICIENCY

This appendix contains example calculations for absorption efficiency adjustments that might be needed for Superfund site risk assessments. Absorption adjustments might be necessary in the risk characterization step to ensure that the site exposure estimate and the toxicity value for comparison are both expressed as absorbed doses or both expressed as intakes.

Information concerning absorption efficiencies might be found in the sections describing absorption toxicokinetics in HEAs, HEEDs, HEEPs, HADs, EPA drinking water quality criteria or ambient water quality criteria documents, or in ATSDR toxicological profiles. If there is no information on absorption efficiency by the oral/inhalation routes, one can attempt to find absorption efficiencies for chemically related substances. If no information is available, conservative default assumptions might be used. Contact ECAO for further guidance.

Adjustments may be necessary to match the exposure estimate with the toxicity value if one is based on an absorbed dose and the other is based on an intake (i.e., administered dose). Adjustments may also be necessary for different vehicles of exposure (e.g., water, food, or soil).

For the dermal route of exposure, the procedures outlined in Chapter 6 result in an estimate of the absorbed dose. Toxicity values that are expressed as administered doses will need to be adjusted to absorbed doses for comparison. This adjustment is discussed in Section A.1.

For the other routes of exposure (i.e., oral and inhalation), the procedures outlined in Chapter 6 result in an estimate of daily intakes. If the toxicity value for comparison is expressed as an administered dose, no adjustment may be necessary (except, perhaps, for vehicle of exposure). If the toxicity value is expressed as an absorbed dose, however, adjustment of the exposure estimate (i.e., intake) to an absorbed dose is needed for comparison with the toxicity value. This adjustment is discussed in Section A.2.

Adjustments also may be necessary for different absorption efficiencies depending on the medium of exposure (e.g., contaminants ingested with food or soil might be less completely absorbed than contaminants ingested with water). This adjustment is discussed in Section A.3.

A.1 ADJUSTMENTS OF TOXICITY VALUE FROM ADMINISTERED TO ABSORBED DOSE

Because there are few, if any, toxicity reference

ACRONYMS FOR APPENDIX A

ATSDR = Agency for Toxic Substances and Disease Registry
ECAO = Environmental Criteria and Assessment Office
HAD = Health Assessment Document
HEA = Health Effects Assessment
HEED = Health and Environmental Effects Document
HEEP = Health and Environmental Effects Profile
RfD = Reference Dose

DEFINITIONS FOR APPENDIX A

Absorbed Dose. The amount of a substance penetrating the exchange boundaries of an organism after contact. Absorbed dose is calculated from the intake and the absorption efficiency, and it usually is expressed as mass of a substance absorbed into the body per unit body weight per unit time (e.g., mg/kg-day).

Administered Dose. The mass of substance administered to an organism and in contact with an exchange boundary (e.g., gastrointestinal tract) per unit body weight per unit time (e.g., mg/kg-day).

Exposure Route. The way a chemical or physical agent comes in contact with an organism (i.e., by ingestion, inhalation, or dermal contact).

Intake. A measure of exposure expressed as the mass of substance in contact with the exchange boundary per unit body weight per unit time (e.g., mg/kg-day). Also termed the normalized exposure rate, equivalent to administered dose.

Reference Dose (RfD). The Agency's preferred toxicity value for evaluating noncarcinogenic effects resulting from exposures at Superfund sites. See specific entries for chronic RfD, subchronic RfD, and developmental RfD. The acronym RfD, when used without other modifiers, either refers generically to all types of RfDs or specifically to chronic RfDs; it never refers specifically to subchronic or developmental RfDs.

Slope Factor. A plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime. The slope factor is used to estimate an upper-bound probability of an individual developing cancer as a result of

values for dermal exposure, oral values are frequently used to assess risks from dermal exposure. Most RfDs and some slope factors are expressed as the amount of substance administered per unit time and unit body weight, whereas exposure estimates for the dermal route of exposure are eventually expressed as absorbed doses. Thus, for dermal exposure to contaminants in water or in soil, it may be necessary to adjust an oral toxicity value from an administered to an absorbed dose. In the boxes to the right and on the next page are samples of adjustments for an oral RfD and an oral slope factor, respectively. If the oral toxicity value is already expressed as an absorbed dose (e.g., trichloroethylene), it is not necessary to adjust the toxicity value.

In the absence of any information on absorption for the substance or chemically related substances, one must assume an oral absorption efficiency. Assuming 100 percent absorption in an oral administration study that serves as the basis for an RfD or slope factor would be a non-conservative approach for estimating the dermal RfD or slope factor (i.e., depending on the type of chemical, the true absorbed dose might have been much lower than 100 percent, and hence an

EXAMPLE: ADJUSTMENT OF AN ADMINISTERED TO AN ABSORBED DOSE RfD

An oral RfD, unadjusted for absorption, equals 10 mg/kg-day.

Other information (or an assumption) indicates a 20% oral absorption efficiency in the species on which the RfD is based.

The adjusted RfD that would correspond to the absorbed dose would be:

10 mg/kg-day x 0.20 = 2 mg/kg-day.

The adjusted RfD of 2 mg/kg-day would be compared with the amount estimated to be absorbed dermally each day.

absorbed-dose RfD should similarly be much lower or the slope factor should be much higher). For example, some metals tend to be poorly absorbed (less than 5 percent) by the gastrointestinal tract. A relatively conservative assumption for oral absorption in the absence of appropriate information would be 5 percent.

EXAMPLE: ADJUSTMENT OF AN ADMINISTERED TO AN ABSORBED DOSE SLOPE FACTOR

An oral slope factor, unadjusted for absorption equals 1.6 $(mg/kg\text{-}day)^{-1}$.

Other information (or an assumption) indicates a 20% absorption efficiency in the species on which the slope factor is based.

The adjusted slope factor that would correspond to the absorbed dose would be:

$1.6(mg/kg\text{-}day)^{-1}/0.20 = 8\ (mg/kg\text{-}day)^{-1}$.

The adjusted slope factor of 8 $(mg/kg\text{-}day)^{-1}$ would be used to estimate the cancer risk associated with the estimated absorbed

A.2 ADJUSTMENT OF EXPOSURE ESTIMATE TO AN ABSORBED DOSE

If the toxicity value is expressed as an absorbed rather than an administered dose, it may be necessary to convert the exposure estimate from an intake into an absorbed dose for comparison. An example of estimating an absorbed dose from an intake using an absorption efficiency factor is provided in the box in the top right corner. Do not adjust exposure estimates for absorption efficiency if the toxicity values are based on administered doses.

A.3 ADJUSTMENT FOR MEDIUM OF EXPOSURE

EXAMPLE: ADJUSTMENT OF EXPOSURE ESTIMATE TO AN ABSORBED DOSE

The exposure assessment indicates that an individual ingests 40 mg/kg-day of the chemical from locally grown vegetables.

The oral RfD (or slope factor) for the chemical is based on an absorbed, not administered, dose.

The human oral absorption efficiency for the contaminant from food is known or assumed to be 10 percent.

The adjusted exposure, expressed as an absorbed dose for comparison with the RfD (or slope factor), would be:

40 mg/kg-day x 0.10 = 4 mg/kg-day.

If the medium of exposure in the site exposure assessment differs from the medium of exposure assumed by the toxicity value (e.g., RfD values usually are based on or have been adjusted to reflect exposure via drinking water, while the site medium of concern may be soil), an absorption adjustment may, on occasion, be appropriate. For example, a substance might be more completely absorbed following exposure to contaminated drinking water than following exposure to contaminated food or soil (e.g., if the substance does not desorb from soil in the gastrointestinal tract). Similarly, a substance might be more completely absorbed following inhalation of vapors than following inhalation of particulates. The selection of adjustment method will depend upon the absorption efficiency inherent in the RfD or slope factor used for comparison. To adjust a food or soil ingestion exposure estimate to match an RfD or slope factor based on the assumption of drinking water ingestion, an estimate of the relative absorption of the substance from food or soil and from water is needed. A sample calculation is provided in the box on the next page.

In the absence of a strong argument for making this adjustment or reliable information on

EXAMPLE: ADJUSTMENT FOR MEDIUM OF EXPOSURE

The expected human daily intake of the substance in food or soil is estimated to be 10 mg/kg-day.

Absorption of the substance from drinking water is known or assumed to be 90%, and absorption of the substance from food or soil is known or assumed to be 30%.

The relative absorption of the substance in food or soil/drinking water is 0.33 (i.e., 30/90).

The oral intake of the substance, adjusted to be comparable with the oral RfD (based on an administered dose in drinking water), would be:

relative absorption efficiencies, assume that the relative absorption efficiency between food or soil and water is 1.0.

If the RfD or slope factor is expressed as an absorbed dose rather than an administered dose, it is only necessary to identify an absorption efficiency associated with the medium of concern in the site exposure estimate. In the example above, this situation would translate into a relative absorption of 0.3 (i.e., 30/100).

APPENDIX B

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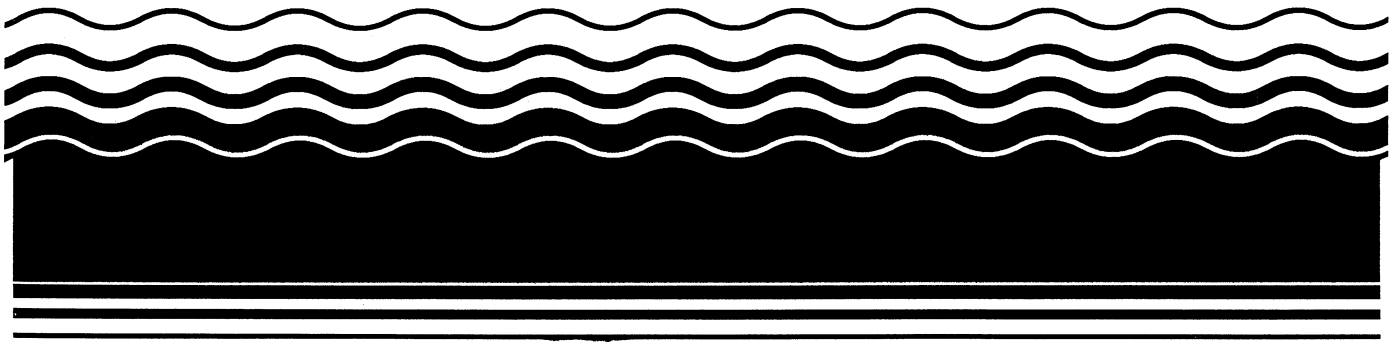
Process for Designing and Conducting Ecological Risk Assessments

Interim Final



ECOLOGICAL RISK ASSESSMENT GUIDANCE FOR SUPERFUND:

PROCESS FOR DESIGNING AND CONDUCTING ECOLOGICAL RISK ASSESSMENTS

INTERIM FINAL

U.S. Environmental Protection Agency
Environmental Response Team
Edison, NJ

June 5, 1997

DISCLAIMER

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U.S. Environmental Protection Agency (U.S. EPA). 1997. *Representative Sampling Guidance Document, Volume 3: Ecological, Draft.* Edison, NJ: Environmental Response Team, Office of Emergency and Remedial Response.

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LIST OF ACRONYMS AND ABBREVIATIONS

AQUIRE:	U.S. EPA's AQUatic Information REtrieval database
ARAR:	Applicable or Relevant and Appropriate Requirements
ASTM:	American Society of Testing and Materials
BAF:	Bioaccumulation Factor
BCF:	Bioconcentration Factor
BIOSIS:	Biosciences Information Services
BTAG:	Biological Technical Assistance Group
CERCLA:	Comprehensive Environmental Response, Compensation, and Liability Act
CLP:	Contract Laboratory Program
DDT:	Dichlorodiphenyltrichloroethane
DQO:	Data Quality Objective
EC_{50}:	Effective Concentration for producing a specified effect in 50 percent of the test organisms
EEC:	Estimated Environmental Concentration
EPA:	Environmental Protection Agency
FS:	Feasibility Study
FSP:	Field Sampling Plan
FWS:	Fish and Wildlife Service
HEAST:	National Center for Environmental Assessment's Health Effects Assessment Summary Tables
HI:	Hazard Index
HQ:	Hazard Quotient
HSDB:	National Library of Medicine's Hazardous Substances Data Bank
IRIS:	EPA's Integrated Risk Information System
LC_{50}:	Concentration Lethal to 50 percent of the test organisms
Li	Liter
LOAEL:	Lowest-Observed-Adverse-Effect Level
NCP:	National Oil and Hazardous Substances Pollution Contingency Plan
NOAA:	National Oceanic and Atmospheric Administration
NOAEL:	No-Observed-Adverse-Effect Level
NRC:	National Research Council
NRDA:	Natural Resource Damage Assessment
OERR:	U.S. EPA Office of Emergency and Remedial Response
OSC:	On-Scene Coordinator
OSWER:	U.S. EPA Office of Solid Waste and Emergency Response
PA	Preliminary Assessment
PAH:	Polycyclic Aromatic Hydrocarbons
PCB:	Polychlorinated Biphenyl compound
PRP:	Potentially Responsible Party
QAPP:	Quality Assurance Project Plan
QA/QC:	Quality Assurance and Quality Control

RBP:	Rapid Bioassessment Protocol
RI:	Remedial Investigation
ROD:	Record of Decision
RPM:	Remedial Project Manager
SAP:	Sampling and Analysis Plan
SARA:	Superfund Amendments and Reauthorization Act of 1986
SI:	Site Investigation
SMDP:	Scientific/Management Decision Point
TOC:	Total Organic Carbon
WP:	Work Plan

PREFACE

This document provides guidance on the process of designing and conducting technically defensible ecological risk assessments for the Superfund Program. It is intended to promote consistency and a science-based approach within the Program and is based on the *Proposed Guidelines for Ecological Risk Assessment* (1996a) and the *Framework for Ecological Risk Assessment* (1992a) developed by the Risk Assessment Forum of the U.S. Environmental Protection Agency. When the Agency publishes its final *Guidelines for Ecological Risk Assessment*, this guidance will be reviewed and revised if necessary to ensure consistency with the Agency guidelines.

This document is directed to the site managers (i.e., On-Scene Coordinators [OSCs] and Remedial Project Managers [RPMs]) who are legally responsible for the management of a site. However, it is anticipated that ecological risk assessors, as well as other individuals with input to the ecological risk assessment, will use this document.

Ecological risk assessment is an integral part of the Remedial Investigation and Feasibility Study (RI/FS) process, which is designed to support risk management decision-making for Superfund sites. The RI component of the process characterizes the nature and extent of contamination at a hazardous waste site and estimates risks to human health and the environment posed by contaminants at the site. The FS component of the process develops and evaluates remedial options. Thus, ecological risk assessment is fundamental to the RI and ecological considerations are also part of the FS process.

This document is intended to facilitate defensible site-specific ecological risk assessments. It is not intended to determine the appropriate scale or complexity of an ecological risk assessment or to direct the user in the selection of specific protocols or investigation methods. Professional judgment is essential in designing and determining the data needs for any ecological risk assessment. However, when the process outlined in this document is followed, a technically defensible and appropriately scaled site-specific ecological risk assessment should result.

Ecological risk assessment is an interdisciplinary field drawing upon environmental toxicology, ecology, and environmental chemistry, as well as other areas of science and mathematics. It is important that users of this document understand that ecological risk assessment is a complex, non-linear process, with many parallel activities. The user should have a basic understanding of ecotoxicology and ecological risk assessment and read through this document in its entirety prior to engaging in the ecological risk assessment process. Without the basic understanding of the field and of this guidance, the reader might not recognize the relationships among different components of the risk assessment process.

To assist the user in interpreting this guidance document, three illustrations of planning an ecological risk assessment for a hazardous waste site are provided in

Appendix A. These are simplified, hypothetical examples that demonstrate and highlight specific points in the ecological risk assessment process. These examples are incomplete and not intended to present a thorough discussion of the ecological or ecotoxicological issues that would exist at an actual site. Instead, they are intended to illustrate the first five steps of the process, which precede a full ecological field investigation. Excerpts from the three examples are included in the guidance document as "Example" boxes to illustrate specific points. The user is encouraged to read the three examples in Appendix A in addition to the Example boxes within the guidance document itself.

Ecological risk assessment is a dynamic field, and this document represents a process framework into which changes in ecological risk assessment approaches can readily be incorporated. Four appendices are included with this document; additional appendices may be developed to address specific issues.

This document supersedes the U.S. EPA's (1989b) *Risk Assessment Guidance for Superfund, Volume 2: Environmental Evaluation Manual* as guidance on how to design and conduct an ecological risk assessment for the Superfund Program. The *Environmental Evaluation Manual* contains useful information on the statutory and regulatory basis of ecological assessment, basic ecological concepts, and other background information that is not repeated in this document.

INTRODUCTION:
ECOLOGICAL RISK ASSESSMENT FOR SUPERFUND

PURPOSE

This document provides guidance on how to design and conduct consistent and technically defensible ecological risk assessments for the Superfund Program. It is based on the *Proposed Guidelines for Ecological Risk Assessment* (1996a) and the *Framework for Ecological Risk Assessment* (1992a) developed by the Risk Assessment Forum of the U.S. Environmental Protection Agency (U.S. EPA or the Agency). When the Agency finalizes its (1996a) *Proposed Guidelines for Ecological Risk Assessment*, this guidance will be reviewed and revised if necessary to ensure consistency with the Agency guidelines.

This document is directed to the site managers (i.e., On-Scene Coordinators [OSCs] and Remedial Project Managers [RPMs]) who are legally responsible for managing site activities. However, it is anticipated that the ecological risk assessors, as well as all other individuals involved with ecological risk assessments, will use this document.

SCOPE

This document is intended to facilitate defensible and appropriately-scaled site-specific ecological risk assessments. It is not intended to dictate the scale, complexity, protocols, data needs, or investigation methods for such assessments. Professional judgment is required to apply the process outlined in this document to ecological risk assessments at specific sites.

BACKGROUND

Superfund Program

The Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund), as amended by the Superfund Amendments and Reauthorization Act of 1986 (SARA), authorizes the U.S. EPA to protect public health and welfare and the environment from the release or potential release of any hazardous substance, pollutant, or contaminant. U.S. EPA's Superfund Program carries out the Agency's mandate under CERCLA/SARA.

The primary regulation issued by U.S. EPA's Superfund Program is the National Oil and Hazardous Substances Pollution Contingency Plan (NCP). The NCP calls for the identification and mitigation of environmental impacts (such as toxicity, bioaccumulation, death, reproductive impairment, growth impairment, and loss of critical habitat) at hazardous waste sites, and for the selection of remedial actions to protect the environment. In addition,

numerous other federal and state laws and regulations concerning environmental protection can be designated under Superfund as "applicable" or "relevant and appropriate" requirements (ARARs) for particular sites. Compliance with these other laws and regulations generally requires an evaluation of site-related ecological effects and the measures necessary to mitigate those effects.

Risk Assessment in Superfund

An important part of the NCP is the requirement for a Remedial Investigation and Feasibility Study (RI/FS) (see Highlight I-1). The RI/FS is an analytical process designed to support risk management decision-making for Superfund sites. The RI component of the process characterizes the nature and extent of contamination at a hazardous waste site and estimates risks to human health and the environment posed by contaminants at the site. The FS component of the process develops and evaluates remedial options.

HIGHLIGHT I-1
The RI/FS Process

Risk assessment is an integral part of the RI/FS. The three parts of the RI are: (1) characterization of the nature and extent of contamination; (2) ecological risk assessment; and (3) human health risk assessment. The investigation of the nature and extent of contamination determines the chemicals present on site as well as their distribution and concentrations. The ecological risk and human health risk assessments determine the potential for adverse effects to the environment and human health, respectively.

Although U.S. EPA has established detailed guidelines for human health risk assessment in the Superfund program (U.S. EPA, 1989a, 1991a,b), similarly detailed guidelines for site-specific ecological risk assessment do not exist for the Superfund program. *Risk Assessment Guidance for Superfund, Volume 2: Environmental Evaluation Manual* (U.S. EPA, 1989b) provides conceptual guidance in planning studies to evaluate a hazardous waste site's "environmental resources" (as used in the manual, the phrase "environmental resources" is largely synonymous with "ecological resources"). U.S. EPA also is publishing supplemental information on specific ecological risk assessment topics for Superfund in the *ECO Update* series (U.S. EPA, 1995b, 1994b,c,d,e, 1992b,c,d, 1991c,d). However, those documents do not describe an overall, step-by-step process by which an ecological risk assessment is designed and executed. The Agency's *Framework for Ecological Risk Assessment* (U.S. EPA, 1992a) provides a basic structure and a consistent approach for conducting ecological risk assessments, but is not intended to provide program-specific guidance. The *Guidelines for Ecological Risk Assessment*, currently being developed by the Agency's Risk Assessment Forum (1996a), will expand on the *Framework*, but again, will not provide program-specific guidance.

This document outlines a step-by-step ecological risk assessment process that is both specific to the Superfund Program and consistent with the more general U.S. EPA *Framework* and guidelines under development. While the Agency's *Framework* and future Agency-wide ecological risk assessment guidelines are not enforceable regulations, the concepts in those

documents are appropriate to Superfund. The concepts in the published *Framework* have been incorporated into this document with minimal modification. The definitions of terms used in this ecological risk assessment guidance for Superfund (and listed in the Glossary) are consistent with the definitions in the U.S. EPA *Framework* document unless noted otherwise.

DEFINITION OF ECOLOGICAL RISK ASSESSMENT

U.S. EPA "Framework" Document

Ecological risk assessment is defined in the *Framework* as a process that evaluates the likelihood that adverse ecological effects are occurring or may occur as a result of exposure to one or more stressors (U.S. EPA, 1992a). The *Framework* defines a stressor as any physical, chemical, or biological entity that can induce an adverse ecological response. Adverse responses can range from sublethal chronic effects in individual organisms to a loss of ecosystem function. Although stressors can be biological (e.g., introduced species), only chemical or physical stressors will be addressed in this document, because these are the stressors subject to risk management decisions at Superfund sites.

Superfund Program

The phrase "ecological risk assessment," as used specifically for the Superfund Program in this document, refers to a qualitative and/or quantitative appraisal of the actual or potential impacts of contaminants from a hazardous waste site on plants and animals other than humans and domesticated species. A risk does not exist unless: (1) the stressor has the ability to cause one or more adverse effects, and (2) it co-occurs with or contacts an ecological component long enough and at a sufficient intensity to elicit the identified adverse effect.

THE ECOLOGICAL RISK ASSESSMENT PROCESS

U.S. EPA "Framework" Document

The *Framework* describes the basic elements of a process for scientifically evaluating the adverse effects of stressors on ecosystems and components of ecosystems. The document describes the basic process and principles to be used in ecological risk assessments conducted for the U.S. EPA, provides operational definitions for terms used in ecological risk assessments, and outlines basic principles around which program-specific guidelines for ecological risk assessment should be organized.

The *Framework* is similar to the National Research Council's (NRC) paradigm for human health risk assessments (NRC, 1983) and the more recent NRC ecological risk paradigm (NRC, 1993). The 1983 NRC paradigm consists of four fundamental phases:

hazard identification, dose-response assessment, exposure assessment, and risk characterization. The *Framework* differs from the 1983 NRC paradigm in a few ways:

- Problem formulation is incorporated into the beginning of the process to determine the focus and scope of the assessment;
- Hazard identification and dose-response assessment are combined in an ecological effects assessment phase; and
- The phrase "dose-response" is replaced by "stressor-response" to emphasize the possibility that physical changes (which are not measured in "doses") as well as chemical contamination can stress ecosystems.

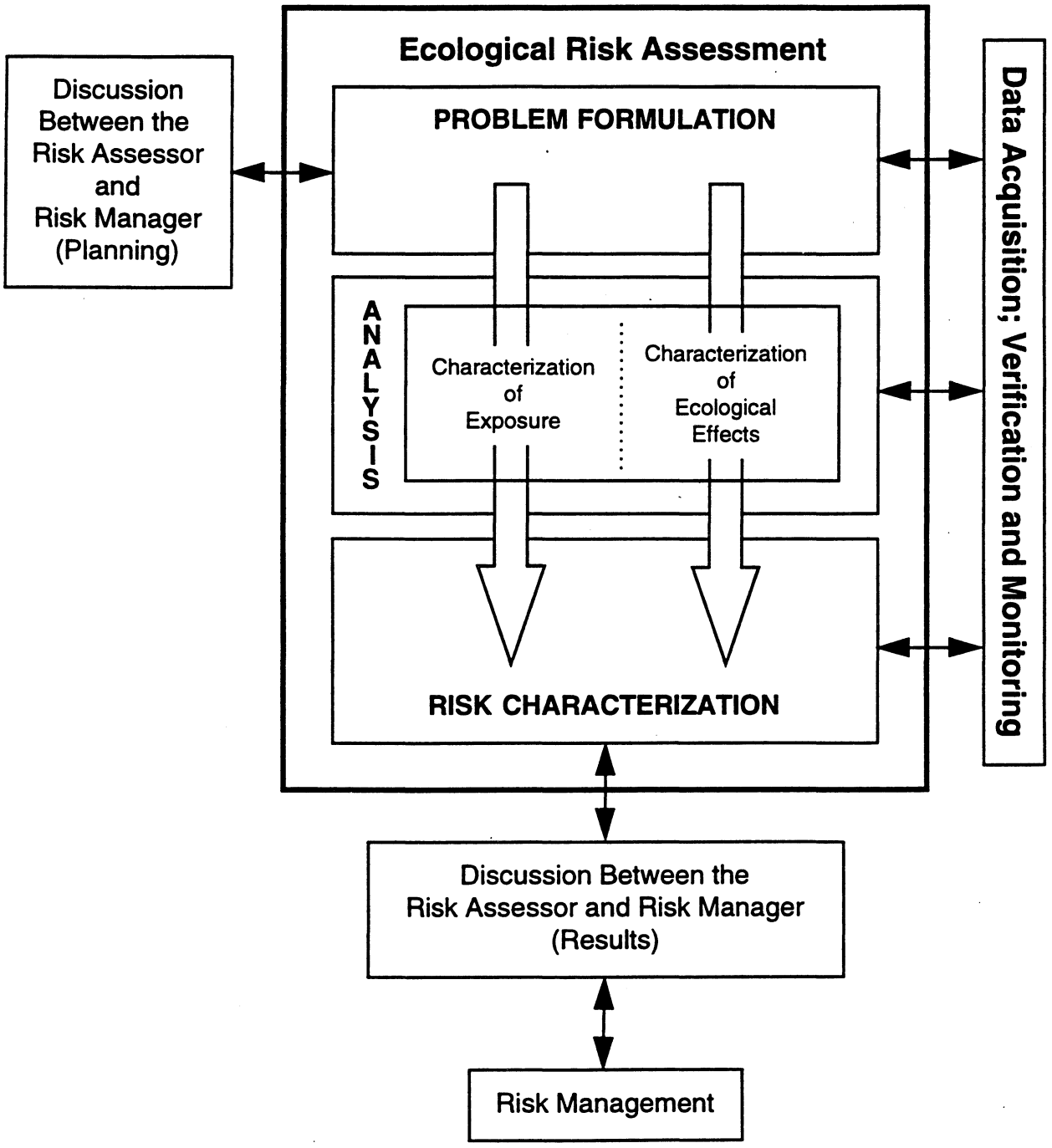
Moreover, the *Framework* emphasizes the parallel nature of the ecological effects and exposure assessments by joining the two assessments in an analysis phase between problem formulation and risk characterization, as shown in Exhibit I-1.

During problem formulation, the risk assessor establishes the goals, breadth, and focus of the assessment (U.S. EPA, 1992a). As indicated in the *Framework*, problem formulation is a systematic planning step that identifies the major factors to be considered and is linked to the regulatory and policy contexts of the assessment. Problem formulation includes discussions between the risk assessor and risk manager, and other involved parties, to identify the stressor characteristics, ecosystems potentially at risk, and ecological effects to be evaluated. During problem formulation, assessment and measurement endpoints for the ecological risk assessment are identified, as described below.

The Agency defines assessment endpoints as explicit expressions of the actual environmental values (e.g., ecological resources) that are to be protected (U.S. EPA, 1992a). Valuable ecological resources include those without which ecosystem function would be significantly impaired, those providing critical resources (e.g., habitat, fisheries), and those perceived as valuable by humans (e.g., endangered species and other issues addressed by legislation). Because assessment endpoints focus the risk assessment design and analysis, appropriate selection and definition of these endpoints are critical to the utility of a risk assessment.

Assessment endpoints should relate to statutory mandates (e.g., protection of the environment), but must be specific enough to guide the development of the risk assessment study design at a particular site. Useful assessment endpoints define both the valued ecological entity at the site (e.g., a species, ecological resource, or habitat type) and a characteristic(s) of the entity to protect (e.g., reproductive success, production per unit area, areal extent). Highlight I-2 provides some examples of specific assessment endpoints related to the general goal of protecting aquatic ecosystems.

EXHIBIT I-1
Ecological Risk Assessment Framework (U.S. EPA, 1992a)



A measurement endpoint is a measurable biological response to a stressor that can be related to the valued characteristic chosen as the assessment endpoint (U.S. EPA, 1992a; although this definition may change—see U.S. EPA, 1996a). Sometimes, the assessment endpoint can be measured directly; usually, however, an assessment endpoint encompasses too many species or species that are difficult to evaluate (e.g., top-level predators). In these cases, the measurement endpoints are different from the assessment endpoint, but can be used to make inferences about risks to the assessment endpoints. For example, measures of responses in particularly sensitive species and life stages might be used to infer responses in the remaining species and life stages in a specific community. Such inferences must be clearly described to demonstrate the link between measurement and assessment endpoints. Highlight I-3 provides examples of measurement endpoints.

HIGHLIGHT I-2
Example Assessment Endpoints

- Sustained aquatic community structure, including species composition and relative abundance and trophic structure.
- Sufficient rates of survival, growth, and reproduction to sustain populations of carnivores typical for the area.
- Sustained fishery diversity and abundance.

Measures of exposure also can be used to make inferences about risks to assessment endpoints at Superfund sites. For example, measures of water concentrations of a contaminant can be compared with concentrations known from the literature to be lethal to sensitive aquatic organisms to infer something about risks to aquatic community structure. As a consequence, for purposes of this guidance, measurement endpoints include both measures of effect and measures of exposure.

A product of problem formulation is a conceptual model for the ecological risk assessment that describes how a given stressor might affect ecological components of the environment. The conceptual model also describes questions about how stressors affect the assessment endpoints, the relationships among the assessment and measurement endpoints, the data required to answer the questions, and the methods that will be used to analyze the data (U.S. EPA, 1992a).

HIGHLIGHT I-3
Example Measurement Endpoints

- Community analysis of benthic macroinvertebrates.
- Survival and growth of fish fry in response to exposure to copper.
- Community structure of fishery in proximity to the site.

Superfund Program

The goal of the ecological risk assessment process in the Superfund Program is to provide the risk information necessary to assist risk managers at Superfund sites (OSCs and RPMs) in making informed decisions regarding substances designated as hazardous under CERCLA (see 40 CFR 302.4). The specific objectives of the process, as stated in OSWER Directive 9285.7-17, are: (1) to identify and characterize the current and potential threats to the environment from a hazardous substance release; and (2) to identify cleanup levels that would protect those natural resources from risk. Threats to the environment include existing adverse ecological impacts and the risk of such impacts in the future. Highlight I-4 provides an overview of ecological risk assessment in the Superfund Program.

Problem formulation is the most critical step of an ecological risk assessment and must precede any attempt to design a site investigation and analysis plan. To ensure that the risk manager can use the results of an ecological risk assessment to inform risk management decisions for a Superfund site, it is important that all involved parties contribute to the problem formulation phase and that the risk manager is clearly identified to all parties. These parties include the remedial project manager (RPM), who is the risk manager with ultimate responsibility for the site, the ecological risk assessment team, the Regional Superfund Biological Technical Assistance Group (BTAG), potentially responsible parties (PRPs), Natural Resource Trustees, and stakeholders in the natural resources at issue (e.g., local communities, state agencies) (U.S. EPA, 1994a, 1995b). The U.S. EPA's (1994a) *Edgewater Consensus on an EPA Strategy for Ecosystem Protection* in particular calls for the Agency to develop a "place-driven" orientation, that is, to focus on the environmental needs of specific communities and ecosystems, rather than on piecemeal program mandates. Participation in problem formulation by all involved parties helps to achieve the place-driven focus.

Issues such as restoration, mitigation, and replacement are important to the Superfund Program, but are reserved for investigations that might or might not be included in the RI phase. During the risk management process of selecting the preferred remedial option leading to the Record of Decision (ROD), issues of mitigation and restoration should be addressed. In selecting a remedy, the risk manager must also consider the degree to which the remedial alternatives reduce risk and thereby also reduce the need for restoration or mitigation.

A natural resource damage assessment (NRDA) may be conducted at a Superfund site at the discretion of Natural Resource Trustees for specific resources associated with a site. An ecological risk assessment is a necessary step for an NRDA, because it establishes the causal link between site contaminants and specific adverse ecological effects. The risk assessment also can provide information on what residual risks are likely for different remediation options. However, the ecological risk assessment does not constitute an NRDA. The NRDA is the sole responsibility of the Natural Resource Trustees, not of the U.S. EPA; therefore, NRDAs will not be addressed in this guidance. For additional information on the role of Natural Resource Trustees in the Superfund process, see *ECO Update Volume 1, Number 3* (U.S. EPA, 1992c).

HIGHLIGHT I-4
Ecological Impact and Risk Assessment

Ecological risk assessment within the Superfund Program can be a risk evaluation (potentially predictive), impact evaluation, or a combination of those approaches. The functions of the ecological risk assessment are to:

(1) Document whether actual or potential ecological risks exist at a site;

(2) Identify which contaminants present at a site pose an ecological risk; and

(3) Generate data to be used in evaluating cleanup options.

Ecological risk assessments can have their greatest influence on risk management at a site in the evaluation and selection of site remedies. The ecological risk assessment should identify contamination levels that bound a threshold for adverse effects on the assessment endpoint. The threshold values provide a yardstick for evaluating the effectiveness of remedial options and can be used to set cleanup goals if appropriate.

To justify a site action based upon ecological concerns, the ecological risk assessment must establish that an actual or potential ecological threat exists at a site. The potential for (i.e., risk of) impacts can be the threat of impacts from a future release or redistribution of contaminants, which could be avoided by taking actions on "hot spots" or source areas. Risk also can be viewed as the likelihood that current impacts are occurring (e.g., diminished population size), although this can be difficult to demonstrate. For example, it may not be practical or technically possible to document existing ecological impacts, either due to limited technique resolution, the localized nature of the actual impact, or limitations resulting from the biological or ecological constraints of the field measurements (e.g., measurement endpoints, exposure point evaluation). Actually demonstrating existing impacts confirms that a "risk" exists. Evaluating a gradient of existing impacts along a gradient of contamination can provide an stressor-response assessment that helps to identify cleanup levels.

As noted above, the ecological risk assessment should provide the information needed to make risk management decisions (e.g., to select the appropriate site remedy). A management option should not be selected first, and then the risk assessment tailored to justify the option.

This Guidance Document

This ecological risk assessment guidance for Superfund is composed of eight steps (see Exhibit I-2) and several scientific/management decision points (SMDPs) (see Exhibit I-3). An SMDP requires a meeting between the risk manager and risk assessment team to evaluate and approve or redirect the work up to that point. (Consultation with the Regional BTAG is recommended for SMDPs (a) through (d) in Exhibit I-3.) The group decides

EXHIBIT I-2
Eight-step Ecological Risk Assessment Process for Superfund

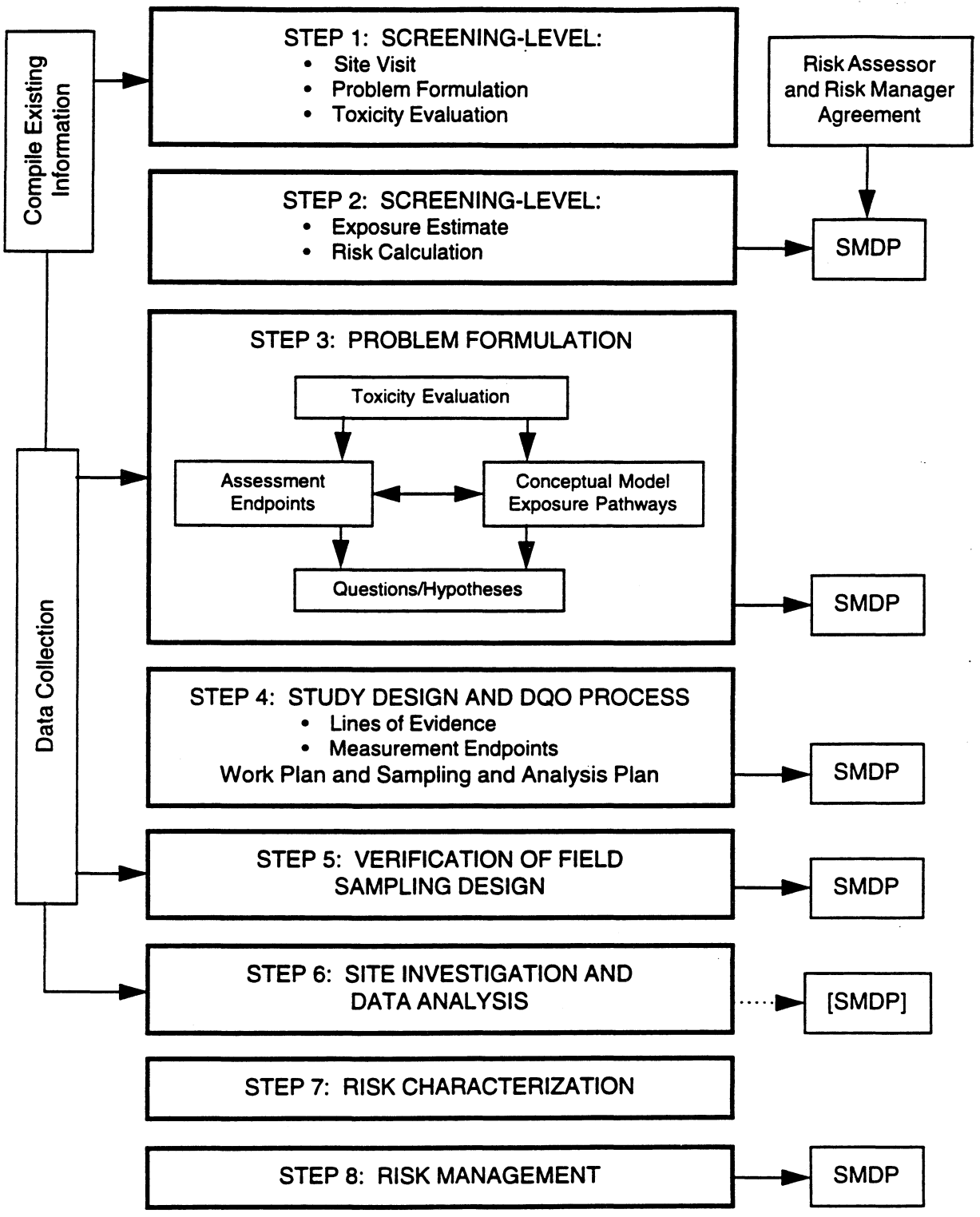


EXHIBIT I-3
Steps in the Ecological Risk Assessment Process and Corresponding Decision Points in the Superfund Process

Steps and Scientific/Management Decision Points (SMDPs):

1.	Screening-Level Problem Formulation and Ecological Effects Evaluation	
2.	Screening-Level Preliminary Exposure Estimate and Risk Calculation	SMDP (a)
3.	Baseline Risk Assessment Problem Formulation	SMDP (b)
4.	Study Design and Data Quality Objectives	SMDP (c)
5.	Field Verification of Sampling Design	SMDP (d)
6.	Site Investigation and Analysis of Exposure and Effects	[SMDP]
7.	Risk Characterization	
8.	Risk Management	SMDP (e)

Corresponding Decision Points in the Superfund Process:

(a) Decision about whether a full ecological risk assessment is necessary.

(b) Agreement among the risk assessors, risk manager, and other involved parties on the conceptual model, including assessment endpoints, exposure pathways, and questions or risk hypotheses.

(c) Agreement among the risk assessors and risk manager on the measurement endpoints, study design, and data interpretation and analysis.

(d) Signing approval of the work plan and sampling and analysis plan for the ecological risk assessment.

(e) Signing the Record of Decision.

[SMDP] only if change to the sampling and analysis plan is necessary.

whether or not the risk assessment is proceeding in a direction that is acceptable to the risk assessors and manager. The SMDPs include a discussion of the uncertainty associated with the risk assessment, that might be reduced, if necessary, with increased effort. SMDPs are significant communication points which should be passed with the consensus of all involved parties. The risk manager should expect deliverables that document specific SMDPs as outlined in Exhibit I-4. This approach is intended to minimize both the cost of and time required for the Superfund risk assessment process.

This guidance provides a technically valid approach for ecological risk assessments at hazardous waste sites, although other approaches also can be valid. The discipline of ecological risk assessment is dynamic and continually evolving; the assessments rely on data that are complex and sometimes ambiguous. Thus, if an approach other than the one described in this guidance document is used, there must be clear documentation of the process, including process design and interpretation of the results, to ensure a technically defensible assessment. Clear documentation, consistency, and objectivity in the assessment process are necessary for the Superfund Program.

An interdisciplinary team including, but not limited to, biologists, ecologists, and environmental toxicologists, is needed to design and implement a successful risk assessment and to evaluate the weight of the evidence obtained to reach conclusions about ecological risks. Some of the many points at which the Superfund ecological risk assessment process requires professional judgment include:

EXHIBIT I-4
Ecological Risk Assessment Deliverables for the Risk Manager

If the process stops at the end of Step 2:

(1) Full documentation of the screening-level assessment and SMDP not to continue the assessment.

If the process continues to Step 3:

(1) Documentation of the conceptual model, including assessment endpoints, exposure pathways, risk hypotheses, and SMDP at the end of Step 3.

(2) The approved and signed work plan and sampling and analysis plan, documenting the SMDPs at the end of Steps 4 and 5.

(3) The baseline risk assessment documentation (including documentation of the screening-level assessment used in the baseline assessment) developed in Step 7.

- Determining the level of effort needed to assess ecological risk at a particular site;

- Determining the relevance of available data to the risk assessment;

- Designing a conceptual model of the ecological threats at a site and measures to assess those threats;

- Selecting methods and models to be used in the various components of the risk assessment;

- Developing assumptions to fill data gaps for toxicity and exposure assessments based on logic and scientific principles; and

- Interpreting the ecological significance of observed or predicted effects.

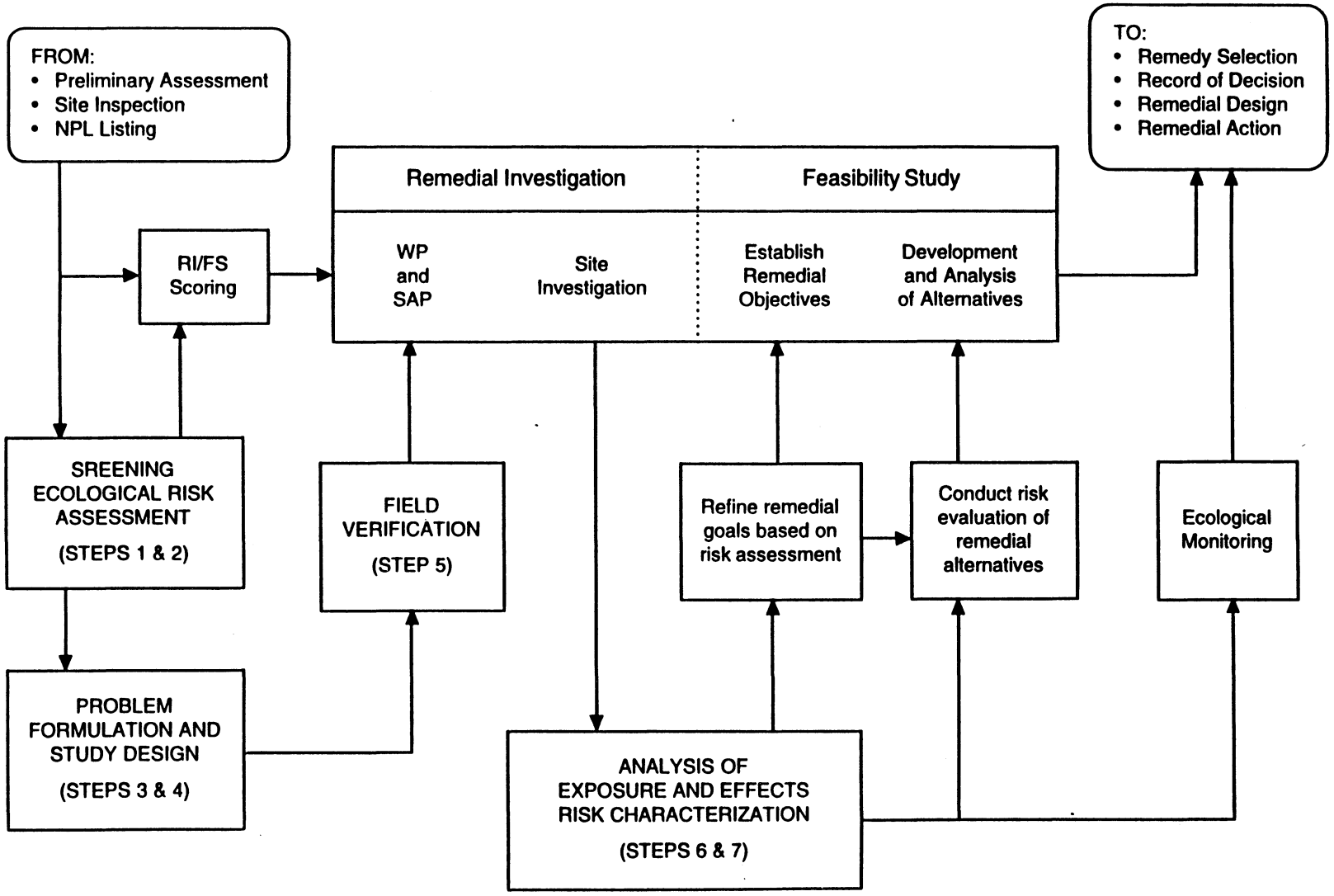
The lead risk assessor should coordinate with appropriate professionals to make many of these decisions. Specialists are needed for the more technical questions concerning the risk assessment (e.g., which model, which assumptions).

This guidance document focuses on the risk assessment process in Superfund and does not address all of the issues that a risk manager will need to consider. After the risk assessment is complete, the risk manager might require additional professional assistance in interpreting the implications of the baseline ecological risk assessment and selecting a remedial option.

The risk assessment process must be structured to ensure that site management decisions can be made without the need for repeated studies or delays. The first two steps in the assessment process are a streamlined version of the complete *Framework* process and are intended to allow a rapid determination by the risk assessment team and risk manager that the site poses no or negligible ecological risk, or to identify which contaminants and exposure pathways require further evaluation. Steps 3 through 7 are a more detailed version of the complete *Framework* process.

The ecological risk assessment process should be coordinated with the overall RI/FS process to the extent possible. Overall site-assessment costs are minimized when the needs of the ecological and human health risk assessments are incorporated into the chemical sampling program to determine the nature and extent of contamination during the RI. For sites at which an RI has not yet been planned or conducted, Exhibit I-5 illustrates the relationship between the eight ecological risk assessment steps and the overall Superfund process and decision points. For older sites at which an RI was conducted before an ecological risk assessment was considered, the ecological risk assessment process should build on the information already developed for the site.

EXHIBIT I-5
Ecological Risk Assessment in the RI/FS Process



It is important to realize that this eight-step approach is not a simple linear or sequential process. The order of actions taken will depend upon the stage of the RI/FS atwhich the site is currently, the amount and types of site information available, as well as other factors. The process can be iterative, and in some iterations, certain individual steps might not be needed. In many cases, it might be appropriate and desirable to conduct several steps concurrently.

Tasks that should be accomplished in each of the eight steps in Exhibits I-2 and I-3 are described in the eight following sections. The eight sections include example boxes based on the three hypothetical Superfund sites in Appendix A as well as exhibits and highlight boxes.

STEP 1: SCREENING-LEVEL PROBLEM FORMULATION AND ECOLOGICAL EFFECTS EVALUATION

OVERVIEW

The screening-level problem formulation and ecological effects evaluation is part of the initial ecological risk screening assessment. For this initial step, it is likely that site-specific information for determining the nature and extent of contamination and for characterizing ecological receptors at the site is limited. This step includes all the functions of problem formulation (more fully described in Steps 3 and 4) and ecological effects analysis, but on a screening level. The results of this step will be used in conjunction with exposure estimates in the preliminary risk calculation in Step 2.

1.1 INTRODUCTION

Step 1 is the screening-level problem formulation process and ecological effects evaluation (Highlight 1-1 defines screening-level risk assessments). Consultation with the BTAG is recommended at this stage. How to brief the BTAG on the setting, history, and ecology of a site is described in *ECO Update Volume 1, Number 5* (U.S. EPA, 1992d). Section 1.2 describes the screening-level problem formulation, and Section 1.3 describes the screening-level ecological effects evaluation. Section 1.4 summarizes this step.

1.2 SCREENING-LEVEL PROBLEM FORMULATION

For the screening-level problem formulation, the risk assessor develops a conceptual model for the site that addresses five issues:

(1) Environmental setting and contaminants known or suspected to exist at the site (Section 1.2.1);

(2) Contaminant fate and transport mechanisms that might exist at the site (Section 1.2.2);

(3) The mechanisms of ecotoxicity associated with contaminants and likely categories of receptors that could be affected (Section 1.2.3);

(4) What complete exposure pathways might exist at the site (a complete exposure pathway is one in which the chemical can be traced or expected to travel from the source to a receptor that can be affected by the chemical) (Section 1.2.4); and

(5) Selection of endpoints to screen for ecological risk (Section 1.2.5).

HIGHLIGHT 1-1
Screening-level Risk Assessments

Screening-level risk assessments are simplified risk assessments that can be conducted with limited data by assuming values for parameters for which data are lacking. At the screening level, it is important to minimize the chances of concluding that there is no risk when in fact a risk exists. Thus, for exposure and toxicity parameters for which site-specific information is lacking, assumed values should consistently be biased in the direction of overestimating risk. This ensures that sites that might pose an ecological risk are studied further. Without this bias, a screening evaluation could not provide a defensible conclusion that negligible ecological risk exists or that certain contaminants and exposure pathways can be eliminated from consideration.

1.2.1 Environmental Setting and Contaminants at the Site

To begin the screening-level problem formulation, there must be at least a rudimentary knowledge of the potential environmental setting and chemical contamination at the site. The first step is to compile information from the site history and from reports related to the site, including the Preliminary Assessment (PA) or Site Investigation (SI). The second step is to use the environmental checklist presented in *Representative Sampling Guidance Document, Volume 3: Ecological* (U.S. EPA, 1997; see Appendix B) to begin characterizing the site for problem formulation. Key questions addressed by the checklist include:

- What are the on- and off-site land uses (e.g., industrial, residential, or undeveloped; current and future)?
- What type of facility existed or exists at the site?
- What are the suspected contaminants at the site?
- What is the environmental setting, including natural areas (e.g., upland forest, on-site stream, nearby wildlife refuge) as well as disturbed/man-made areas (e.g., waste lagoons)?
- Which habitats present on site are potentially contaminated or otherwise disturbed?

- Has contamination migrated from source areas and resulted in "off-site" impacts or the threat of impacts in addition to on-site threats or impacts?

These questions should be answered using the site reports, maps (e.g, U.S. Geological Survey, National Wetlands Inventory), available aerial photographs, communication with appropriate agencies (e.g., U.S. Fish and Wildlife Service, National Oceanic and Atmospheric Administration, State Natural Heritage Programs), and a site visit. Activities that should be conducted during the site visit include:

- Note the layout and topography of the site;
- Note and describe any water bodies and wetlands;
- Identify and map evidence indicating contamination or potential contamination (e.g., areas of no vegetation, runoff gullies to surface waters);
- Describe existing aquatic, terrestrial, and wetland ecological habitat types (e.g., forest, old field), and estimate the area covered by those habitats;
- Note any potentially sensitive environments (see Section 1.2.3 for examples of sensitive environments);
- Describe and, if possible, map soil and water types, land uses, and the dominant vegetation species present; and
- Record any observations of animal species or sign of a species.

Mapping can be useful in establishing a "picture" of the site to assist in problem formulation. The completed checklist (U.S. EPA, 1997) will provide information regarding habitats and species potentially or actually present on site, potential contaminant migration pathways, exposure pathways, and the potential for non-chemical stresses at the site.

After finishing the checklist, it might be possible to determine that present or future ecological impacts are negligible because complete exposure pathways do not exist and could not exist in the future. Many Superfund sites are located in highly industrialized areas where there could be few if any ecological receptors or where site-related impacts might be indistinguishable from non-site-related impacts (see Highlight 1-2). For such sites, remediation to reduce ecological risks might not be needed. However, all sites should be evaluated by qualified personnel to determine whether this conclusion is appropriate.

Other Superfund sites are located in less disturbed areas with protected or sensitive environments that could be at risk of adverse effects from contaminants from the site. State and federal laws (e.g., the Clean Water Act, the Endangered Species Act) designate certain types of environments as requiring protection. Other types of habitats unique to certain areas

also could need special consideration in the risk assessment (see Section 1.2.3).

1.2.2 Contaminant Fate and Transport

During problem formulation, pathways for migration of a contaminant (e.g., windblown dust, surface water runoff, erosion) should be identified. These pathways can exhibit a decreasing gradient of contamination with increasing distance from a site. There are exceptions, however, because physical and chemical characteristics of the media also influence contaminant distribution (e.g., the pattern of sediment deposition in streams varies depending on stream flow and bottom characteristics). For the screening-level risk assessment, the highest contaminant concentrations measured on the site should be documented for each medium.

HIGHLIGHT 1-2
Industrial or Urban Settings

Many hazardous waste sites exist in currently or historically industrialized or urbanized areas. In these instances, it can be difficult to distinguish between impacts related to contaminants from a particular site and impacts related to non-contaminant stressors or to contaminants from other sites. However, even in these cases, it could be appropriate to take some remedial actions based on ecological risks. These actions might be limited to source removal or might be more extensive. An ecological risk assessment can assist the risk manager in determining what action, if any, is appropriate.

1.2.3 Ecotoxicity and Potential Receptors

Understanding the toxic mechanism of a contaminant helps to evaluate the importance of potential exposure pathways (see Section 1.2.4) and to focus the selection of assessment endpoints (see Section 1.2.5). Some contaminants, for example, affect primarily vertebrate animals by interfering with organ systems not found in invertebrates or plants (e.g., distal tubules of vertebrate kidneys, vertebrate hormone systems). Other substances might affect primarily certain insect groups (e.g., by interfering with hormones needed for metamorphosis), plants (e.g., herbicides), or other groups of organisms. For substances that affect, for example, reproduction of mammals at much lower environmental exposure levels than they affect other groups of organisms, the screening-level risk assessment can initially focus on exposure pathways and risks to mammals. Example 1-1 illustrates this point using the PCB site example provided in Appendix A. A review of some of the more recent ecological risk and toxicity assessment literature can help identify likely effects of the more common contaminants at Superfund sites.

An experienced biologist or ecologist can determine what plants, animals, and habitats exist or can be expected to exist in the area of the Superfund site. Exhibit 1-1, adapted from the Superfund Hazard Ranking System, is a partial list of types of sensitive environments that could require protection or special consideration. Information obtained for the environmental checklist (Section 1.2.1), existing information and maps, and aerial photographs should be used to identify the presence of sensitive environments on or near a site that might be threatened by contaminants from the site.

EXAMPLE 1-1
Ecotoxicity–PCB Site

Some PCBs are reproductive toxins in mammals (Ringer et al., 1972; Aulerich et al., 1985; Wren et al., 1991; Kamrin and Ringer, 1996). When ingested, they induce (i.e., increase concentrations and activity of) enzymes in the liver, which might affect the metabolism of some steroid hormones (Rice and O'Keefe, 1995). Whatever the mechanism of action, several physiological functions that are controlled by steroid hormones can be altered by the exposure of mammals to certain PCBs, and reproduction appears to be the most sensitive endpoint for PCB toxicity in mammals (Rice and O'Keefe, 1995). Given this information, the screening ecological risk assessment should include potential exposure pathways for mammals to PCBs that are reproductive toxins (see Example 1-2).

1.2.4 Complete Exposure Pathways

Evaluating potential exposure pathways is one of the primary tasks of the screening-level ecological characterization of the site. For an exposure pathway to be complete, a contaminant must be able to travel from the source to ecological receptors and to be taken up by the receptors via one or more exposure routes. (Highlight 1-3 defines exposure pathway and exposure route.) Identifying complete exposure pathways prior to a quantitative evaluation of toxicity allows the assessment to focus on only those contaminants that can reach ecological receptors.

Different exposure routes are important for different groups of organisms. For terrestrial animals, three basic exposure routes need to be evaluated: inhalation, ingestion, and dermal absorption. For terrestrial plants, root absorption of contaminants in soils and leaf absorption of contaminants evaporating from the soil or deposited on the leaves are of concern at Superfund sites. For aquatic animals, direct contact (of water or sediment with the gills or integument) and ingestion of food (and sometimes sediments) should be considered. For aquatic plants, direct contact with water, and sometimes with air or sediments, is of primary concern.

The most likely exposure pathways and exposure routes also are related to the physical and chemical properties of the contaminant (e.g., whether or not the contaminant is bound to a matrix, such as organic carbon). Of the basic exposure routes identified above, more information generally is available to quantify exposure levels for ingestion by terrestrial animals and for direct contact with water or sediments by aquatic organisms than for other exposure routes and receptors. Although other exposure routes can be important, more

EXHIBIT 1-1
List of Sensitive Environments in the Hazard Ranking System[a]

Critical habitat for Federal designated endangered or threatened species
Marine Sanctuary
National Park
Designated Federal Wilderness Area
Areas identified under the Coastal Zone Management Act
Sensitive areas identified under the National Estuary Program or Near Coastal Waters Program
Critical areas identified under the Clean Lakes Program
National Monument
National Seashore Recreational Area
National Lakeshore Recreational Area
Habitat known to be used by Federal designated or proposed endangered or threatened species
National Preserve
National or State Wildlife Refuge
Unit of Coastal Barrier Resources System
Coastal Barrier (undeveloped)
Federal land designated for protection of natural ecosystems
Administratively Proposed Federal Wilderness Area
Spawning areas critical for the maintenance of fish/shellfish species within river, lake, or coastal tidal waters
Migratory pathways and feeding areas critical for maintenance of anadromous fish species within river reaches or areas in lakes or coastal tidal waters in which the fish spend extended periods of time
Terrestrial areas utilized for breeding by large or dense aggregations of animals
National river reach designated as Recreational
Habitat known to be used by state designated endangered or threatened species
Habitat known to be used by species under review as to its Federal endangered or threatened status
Coastal Barrier (partially developed)
Federally-designated Scenic or Wild River
State land designated for wildlife or game management
State-designated Scenic or Wild River
State-designated Natural Areas
Particular areas, relatively small in size, important to maintenance of unique biotic communities
State-designated areas for protection or maintenance of aquatic life
Wetlands[b]

[a] The categories are listed in groups from those assigned higher factor values to those assigned lower factor values in the Hazard Ranking System (HRS) for listing hazardous waste sites on the National Priorities List (U.S. EPA, 1990b). See *Federal Register*, Vol. 55, pp. 51624 and 51648 for additional information regarding definitions.

[b] Under the HRS, wetlands are rated on the basis of size. See *Federal Register*, Vol. 55, pp. 51625 and 51662 for additional information.

assumptions are needed to estimate exposure levels for those routes, and the results are less certain. Professional judgment is needed to determine if evaluating those routes sufficiently improves a risk assessment to warrant the effort.

HIGHLIGHT 1-3
Exposure Pathway and Exposure Route

Exposure Pathway: The pathway by which a contaminant travels from a source (e.g., drums, contaminated soils) to receptors. A pathway can involve multiple media (e.g., soil runoff to surface waters and sedimentation, or volatilization to the atmosphere).

Exposure Route: A point of contact/entry of a contaminant from the environment into an organism (e.g., inhalation, ingestion, dermal absorption).

If an exposure pathway is not complete for a specific contaminant (i.e., ecological receptors cannot be exposed to the contaminant), that exposure pathway does not need to be evaluated further. For example, suppose a contaminant that impairs reproduction in mammals occurs only in soils that are well below the root zone of plants that occur or are expected to occur on a site. Herbivorous mammals would not be exposed to the contaminant through their diets because plants would not be contaminated. Assuming that most soil macroinvertebrates available for ingestion live in the root zone, insectivorous mammals also would be unlikely to be exposed. In this case, a complete exposure pathway for this contaminant for ground-dwelling mammals would not exist, and the contaminant would not pose a significant risk to this group of organisms. Secondary questions might include whether the contaminant is leaching from the soil to ground water that discharges to surface water, thereby posing a risk to the aquatic environment or to terrestrial mammals that drink the water or consume aquatic prey. Example 1-2 illustrates the process of identifying complete exposure pathways based on the hypothetical PCB site described in Appendix A.

1.2.5 Assessment and Measurement Endpoints

For the screening-level ecological risk assessment, assessment endpoints are any adverse effects on ecological receptors, where receptors are plant and animal populations and communities, habitats, and sensitive environments. Adverse effects on populations can be inferred from measures related to impaired reproduction, growth, and survival. Adverse effects on communities can be inferred from changes in community structure or function. Adverse effects on habitats can be inferred from changes in composition and characteristics that reduce the habitats' ability to support plant and animal populations and communities.

Many of the screening ecotoxicity values now available or likely to be available in the future for the Superfund program (see Section 1.3) are based on generic assessment endpoints (e.g., protection of aquatic communities from changes in structure or function) and are assumed to be widely applicable to sites around the United States.

EXAMPLE 1-2
Complete Exposure Pathways for Mammals–PCB Site

Three possible exposure pathways for mammals were evaluated at the PCB Site: inhalation, ingestion through the food chain, and incidental soil/sediment ingestion.

Inhalation. PCBs are not highly volatile, so the inhalation of PCB vapors by mammals would be an essentially incomplete exposure pathway. Inhalation of PCBs adsorbed to soil particles might need consideration in areas with exposed soils, but this site is well vegetated.

Ingestion through the food chain. PCBs tend to bioaccumulate and biomagnify in food chains. PCBs in soils are not taken up by most plants, but are accumulated by soil macroinvertebrates. Thus, in areas without significant soil deposition on the surfaces of plants, mammalian herbivores would not be exposed to PCBs in most of their diet. In contrast, mammalian insectivores, such as shrews, could be exposed to PCBs in most of their diet. For PCBs, the ingestion route for mammals would be essentially incomplete for herbivores but complete for insectivores. For the PCB site, therefore, the ingestion exposure route for a mammalian insectivore (e.g., shrew) would be a complete exposure pathway that should be evaluated.

Incidental soil/sediment ingestion. Mammals can ingest some quantity of soils or sediments incidentally, as they groom their fur or consume plants or animals from the soil. Burrowing mammals are likely to ingest greater quantities of soils during grooming than non-burrowing mammals, and mammals that consume plant roots or soil-dwelling macroinvertebrates are likely to ingest greater quantities of soils attached to the surface of their foods than mammals that consume other foods. The intake of PCBs from incidental ingestion of PCB-contaminated soils is difficult to estimate, but for insectivores that forage at ground level, it is likely to be far less than the intake of PCBs in the diet. For herbivores, the incidental intake of PCBs in soils might be higher than the intake of PCBs in their diet, but still less than the intake of PCBs by mammals feeding on soil macroinvertebrates. Thus, the exposure pathway for ground-dwelling mammalian insectivores remains the exposure pathway that should be evaluated.

1.3 SCREENING-LEVEL ECOLOGICAL EFFECTS EVALUATION

The next step in the screening-level risk assessment is the preliminary ecological effects evaluation and the establishment of contaminant exposure levels that represent conservative thresholds for adverse ecological effects. In this guidance, those conservative thresholds are called screening ecotoxicity values. Physical stresses unrelated to contaminants at the site are not the focus of the risk assessment (see Highlight 1-4), although they can be considered later when evaluating effects of remedial alternatives.

A literature search for studies that quantify toxicity (i.e., exposure-response) is necessary to evaluate the likelihood of toxic effects in different groups of organisms. Appendix C provides a basic introduction to conducting a literature search, but an expert should be consulted to minimize time and costs. The toxicity profile should describe the toxic mechanisms of action for the exposure routes being evaluated and the dose or environmental concentration that causes a specified adverse effect.

For each complete exposure pathway, route, and contaminant, a screening ecotoxicity value should be developed.[1] The U.S. EPA Office of Emergency and Remedial Response has developed screening ecotoxicity values [called ecotox threshold values (U.S. EPA, 1996c)]. The values are for surface waters and sediments, and are based on direct exposures routes only; bioaccumulation and biomagnification in food chains have not been accounted for. The following subsections describe preferred data (Section 1.3.1), dose conversions (Section 1.3.2), and analyzing uncertainty in the values (Section 1.3.3).

HIGHLIGHT 1-4
Non-Chemical Stressors

Ecosystems can be stressed by physical, as well as by chemical, alterations of their environment. For this reason, EPA's (1992a) *Framework for Ecological Risk Assessment* addresses "stressor-response" evaluation to include all types of stress instead of "dose-response" or "exposure-response" evaluation, which implies that the stressor must be a toxic substance.

For Superfund sites, however, the baseline risk assessment addresses risks from hazardous substances released to the environment, not risks from physical alterations of the environment, unless caused indirectly by a hazardous substances (e.g., loss of vegetation from a chemical release leading to serious erosion). This guidance document, therefore, focuses on exposure-response evaluations for toxic substances. Physical destruction of habitat that might be associated with a particular remedy is considered in the Feasibility Study.

1.3.1 Preferred Toxicity Data

Screening ecotoxicity values should represent a no-observed-adverse-effect-level (NOAEL) for long-term (chronic) exposures to a contaminant. Ecological effects of most concern are those that can impact populations (or higher levels of biological organization). Those include adverse effects on development, reproduction, and survivorship. Community-level effects also can be of concern, but toxicity data on community-level endpoints are limited and might be difficult to extrapolate from one community to another.

[1] It is possible to conduct a screening risk assessment with limited information and conservative assumptions. If site-specific information is too limited, however, the risk assessment is almost certain to move into Steps 3 through 7, which require field-collected data. The more complete the initial information, the better the decision that can be made at this preliminary stage.

When reviewing the literature, one should be aware of the limitations of published information in characterizing actual or probable hazards at a specific site. U.S. EPA discourages reliance on secondary references because study details relevant for determining the applicability of findings to a given site usually are not reported in secondary sources. Only primary literature that has been carefully reviewed by an ecotoxicologist should be used to support a decision. Several considerations and data preferences are summarized in Highlight 1-5 and described more fully below.

HIGHLIGHT 1-5
Data Hierarchy for Deriving Screening Ecotoxicity Values

To develop a chronic NOAEL for a screening ecotoxicity value from existing literature, the following data hierarchy minimizes extrapolations and uncertainties in the value:

- A NOAEL is preferred to a LOAEL, which is preferred to an LC_{50} or an EC_{50}.
- Long-term (chronic) studies are preferred to medium-term (subchronic) studies, which are preferred to short-term (acute) studies.
- If exposure at the site is by ingestion, dietary studies are preferred to gavage studies, which are preferred to non-ingestion routes of exposure. Similarly, if exposure at the site is dermal, dermal studies are preferred to studies using other exposure routes.

NOAELS and LOAELS. For each contaminant for which a complete exposure pathway/route exists, the literature should be reviewed for the lowest exposure level (e.g., concentration in water or in the diet, ingested dose) shown to produce adverse effects (e.g., reduced growth, impaired reproduction, increased mortality) in a potential receptor species. This value is called a lowest-observed-adverse-effect-level or LOAEL. For those contaminants with documented adverse effects, one also should identify the highest exposure level that is a NOAEL. A NOAEL is more appropriate than a LOAEL to use as an screening ecotoxicity value to ensure that risk is not underestimated (see Highlight 1-6). However, NOAELs currently are not available for many groups of organisms and many chemicals. When a LOAEL value, but not a NOAEL value, is available from the literature, a standard practice is to multiply the LOAEL by 0.1 and to use the product as the screening ecotoxicity value. Support for this practice comes from a data review indicating that 96 percent of chemicals included in the review had LOAEL/NOAEL ratios of five or less, and that all were ten or less (Dourson and Stara, 1983).

Exposure duration. Data from studies of chronic exposure are preferable to data from medium-term (subchronic), short-term (acute), or single-exposure studies because exposures at Superfund remedial sites usually are long-term. Literature reviews by McNamara (1976) and Weil and McCollister (1963) indicate that chronic NOAELs can be

lower than subchronic (90-day duration for rats) NOAELs by up to a factor of ten.[2]

Exposure route. The exposure route and medium used in the toxicity study should be comparable to the exposure route in the risk assessment. For example, data from studies where exposure is by gavage generally are not preferred for estimating dietary concentrations that could produce adverse effects, because the rate at which the substance is absorbed from the gastrointestinal tract usually is greater following gavage than following dietary administration. Similarly, intravenous injection of a substance results in "instantaneous absorption" and does not allow the substance to first pass through the liver, as it would following dietary exposure. If it is necessary to attempt to extrapolate toxicity test results from one route of exposure to another, the extrapolation should be performed or reviewed by a toxicologist experienced in route-to-route extrapolations for the class of animals at issue.

HIGHLIGHT 1-6
NOAEL Preferred to LOAEL

Because the NOAEL and LOAEL are estimated by hypothesis testing (i.e., by comparing the response level of a test group to the response level of a control group for a statistically significant difference), the actual proportion of the test animals showing the adverse response at an identified LOAEL depends on sample size, variability of the response, and the dose interval. LOAELs, and even NOAELs, can represent a 30 percent or higher effect level for the minimum sample sizes recommended for standard test protocols. For this reason, U.S. EPA recommends that the more conservative NOAELs, instead of LOAELs, are used to determine a screening exposure level that is unlikely to adversely impact populations. If dose-response data are available, a site-specific low-effect level may be determined.

Field versus laboratory. Most toxicity studies evaluate effects of a single contaminant on a single species under controlled laboratory conditions. Results from these studies might not be directly applicable to the field, where organisms typically are exposed to more than one contaminant in environmental situations that are not comparable to a laboratory setting and where genetic composition of the population can be more heterogeneous than that of organisms bred for laboratory use. In addition, the bioavailability of a contaminant might be different at a site than in a laboratory toxicity test. In a field situation, organisms also will be subject to other environmental variables, such as unusual weather conditions, infectious diseases, and food shortages. These variables can have either positive or negative effects on

[2] The literature reviews of McNamara (1976) and Weil and McCollister (1963) included both rodent and non-rodent species. The duration of the subchronic exposure usually was 90 days, but ranged from 30 to 210 days. A wide variety of endpoints and criteria for adverse effects were included in these reviews. Despite this variation in the original studies, their findings provide a general indication of the ratio between subchronic to chronic NOAELs for effects other than cancer and reproductive effects. For some chemicals, chronic dosing resulted in increased chemical tolerance. For over 50 percent of the compounds tested, the chronic NOAEL was less than the 90-day NOAEL by a factor of 2 or less. However, in a few cases, the chronic NOAEL was up to a factor of 10 less than the subchronic NOAEL (U.S. EPA, 1993e).

the organism's response to a toxic contaminant that only a site-specific field study would be able to evaluate. Moreover, single-species toxicity tests seldom provide information regarding toxicant-related changes in community interactions (e.g., behavioral changes in prey species that make them more susceptible to predation).

1.3.2 Dose Conversions

For some data reported in the literature, conversions are necessary to allow the data to be used for species other than those tested or for measures of exposure other than those reported. Many doses in laboratory studies are reported in terms of concentration in the diet (e.g., mg contaminant/kg diet or ppm in the diet). Dietary concentrations can be converted to dose (e.g., mg contaminant/kg body weight/day) for comparison with estimated contaminant intake levels in the receptor species.

When converting doses, it is important to identify whether weights are measured as wet or dry weights. Usually, body weights are reported on a wet-weight, not dry-weight basis. Concentration of the contaminant in the diet might be reported on a wet- or dry-weight basis.

Ingestion rates and body weights for a test species often are reported in a toxicity study or can be obtained from other literature sources (e.g., U.S. EPA, 1993a,b). For extrapolations between animal species with different metabolic rates as well as dietary composition, consult U.S. EPA 1992e and 1996b.

1.3.3 Uncertainty Assessment

Professional judgment is needed to determine the uncertainty associated with information taken from the literature and any extrapolations used in developing a screening ecotoxicity value. The risk assessor should be consistently conservative in selecting literature values and describe the limitations of using those values in the context of a particular site. Consideration of the study design, endpoints, and other factors are important in determining the utility of toxicity data in the screening-level risk assessment. All of those factors should be addressed in a brief evaluation of uncertainties prior to the screening-level risk calculation.

1.4 SUMMARY

At the conclusion of the screening-level problem formulation and ecological effects evaluation, the following information should have been compiled:

- Environmental setting and contaminants known or suspected to exist at the site and the maximum concentrations present (for each medium);
- Contaminant fate and transport mechanisms that might exist at the site;

- The mechanisms of ecotoxicity associated with contaminants and likely categories of receptors that could be affected;

- The complete exposure pathways that might exist at the site from contaminant sources to receptors that could be affected; and

- Screening ecotoxicity values equivalent to chronic NOAELs based on conservative assumptions.

For the screening-level ecological risk assessment, assessment endpoints will include any likely adverse ecological effects on receptors for which exposure pathways are complete, as determined from the information listed above. Measurement endpoints will be based on the available literature regarding mechanisms of toxicity and will be used to establish the screening ecotoxicity values. Those values will be used with estimated exposure levels to screen for ecological risks, as described in Step 2.

STEP 2: SCREENING-LEVEL EXPOSURE ESTIMATE AND RISK CALCULATION

OVERVIEW

The screening-level exposure estimate and risk calculation comprise the second step in the ecological risk screening for a site. Risk is estimated by comparing maximum documented exposure concentrations with the ecotoxicity screening values from Step 1. At the conclusion of Step 2, the risk manager and risk assessment team will decide that either the screening-level ecological risk assessment is adequate to determine that ecological threats are negligible, or the process should continue to a more detailed ecological risk assessment (Steps 3 through 7). If the process continues, the screening-level assessment serves to identify exposure pathways and preliminary contaminants of concern for the baseline risk assessment by eliminating those contaminants and exposure pathways that pose negligible risks.

2.1 INTRODUCTION

This step includes estimating exposure levels and screening for ecological risks as the last two phases of the screening-level ecological risk assessment. The process concludes with a SMDP at which it is determined that: (1) ecological threats are negligible; (2) the ecological risk assessment should continue to determine whether a risk exists; or (3) there is a potential for adverse ecological effects, and a more detailed ecological risk assessment, incorporating more site-specific information, is needed.

Section 2.2 describes the screening-level exposure assessment, focusing on the complete exposure pathways identified in Step 1. Section 2.3 describes the risk calculation process, including estimating a hazard quotient, documenting the uncertainties in the quotient, and summarizing the overall confidence in the screening-level ecological risk assessment. Section 2.4 describes the SMDP that concludes Step 2.

2.2 SCREENING-LEVEL EXPOSURE ESTIMATES

To estimate exposures for the screening-level ecological risk calculation, on-site contaminant levels and general information on the types of biological receptors that might be exposed should be known from Step 1. Only complete exposure pathways should be evaluated. For these, the highest measured or estimated on-site contaminant concentration for

each environmental medium should be used to estimate exposures. This should ensure that potential ecological threats are not missed.

2.2.1 Exposure Parameters

For parameters needed to estimate exposures for which sound site-specific information is lacking or difficult to develop, conservative assumptions should be used at this screening level. Examples of conservative assumptions are listed below and described in the following paragraphs:

- Area-use factor – 100 percent (factor related to home range and population density; see Highlight 2-1);
- Bioavailability – 100 percent;
- Life stage – most sensitive life stage;
- Body weight and food ingestion rate – minimum body weight to maximum ingestion rate; and
- Dietary composition – 100 percent of diet consists of the most contaminated dietary component.

HIGHLIGHT 2-1
Area-use Factor

An animal's area-use factor can be defined as the ratio of the area of contamination (or the site area under investigation) to the area used by the animal, e.g., its home range, breeding range, or feeding/foraging range. To ensure that ecological risks are not underestimated, the highest density and smallest area used by each animal should be assumed. This allows the maximum number of animals to be exposed to site contaminants and makes it more likely that "hot spots" (i.e., areas of unusually high contamination levels) will be significant proportions of an individual animal's home range.

Area-use factor. For the screening-level exposure estimate for terrestrial animals, assume that the home range of one or more animals is entirely within the contaminated area, and thus the animals are exposed 100 percent of the time. This is a conservative assumption and, as an assumption, is only applicable to the screening-level phase of the risk assessment. Species- and site-specific home range information would be needed later, in Step 6, to estimate more accurately the percentage of time an animal would use a contaminated area. Also evaluate the possibility that some species might actually focus their activities in contaminated areas of the site. For example, if contamination has reduced emergent vegetation in a pond, the pond might be more heavily used for feeding by waterfowl than uncontaminated ponds with little open water.

Bioavailability. For the screening-level exposure estimate, in the absence of site-specific information, assume that the bioavailability of contaminants at the site is 100 percent. For example, at the screening-level, lead would be assumed to be 100 percent bioavailable to mammals. While some literature indicates that mammals absorb approximately 10 percent of ingested lead, absorption efficiency can be higher, up to about 60 percent, because dietary

factors such as fasting, and calcium and phosphate content of the diet, can affect the absorption rate (Kenzaburo, 1986). Because few species have been tested for bioavailability, and because Steps 3 through 6 provide an opportunity for this issue to be addressed specifically, the most conservative assumption is appropriate for this step.

Life stage. For the screening-level assessment, assume that the most sensitive life stages are present. If an early life stage is the most sensitive, the population should be assumed to include or to be in that life stage. For vertebrate populations, it is likely that most of the population is not in the most sensitive life stage most of the time. However, for many invertebrate species, the entire population can be at an early stage of development during certain seasons.

Body weight and food ingestion rates. Estimates of body weight and food ingestion rates of the receptor animals also should be made conservatively to maximize the dose (intake of contaminants) on a body-weight basis and to avoid understating risk, although uncertainties in these factors are far less than the uncertainties associated with the environmental contaminant concentrations. U.S. EPA's *Wildlife Exposure Factors Handbook* (U.S. EPA, 1993a,b) is a good source or reference to sources of this information.

Bioaccumulation. Bioaccumulation values obtained from a literature search can be used to estimate contaminant accumulation and food-chain transfer at a Superfund site at the screening stage. Because many environmental factors influence the degree of bioaccumulation, sometimes by several orders of magnitude, the most conservative (i.e., highest) bioaccumulation factor (BAF) reported in the literature should be used in the absence of site-specific information.

Dietary composition. For species that feed on more than one type of food, the screening-level assumption should be that the diet is composed entirely of whichever type of food is most contaminated. For example, if some foods (e.g., insects) are likely to be more contaminated than other foods (e.g., seeds and fruits) typical in the diet of a receptor species, assume that the receptor species feeds exclusively on the more contaminated type of food. Again, EPA's *Wildlife Exposure Factors Handbook* (U.S. EPA, 1993a,b) is a good source or reference to sources of this information.

2.2.2 Uncertainty Assessment

Professional judgment is needed to determine the uncertainty associated with information taken from the literature and any extrapolations used in developing a parameter to estimate exposures. All assumptions used to estimate exposures should be stated, including some description of the degree of bias possible in each. Where literature values are used, an indication of the range of values that could be considered appropriate also should be indicated.

2.3 SCREENING-LEVEL RISK CALCULATION

A quantitative screening-level risk can be estimated using the exposure estimates developed according to Section 2.2 and the screening ecotoxicity values developed according to Section 1.3. For the screening-level risk calculation, the hazard quotient approach, which compares point estimates of screening ecotoxicity values and exposure values, is adequate to estimate risk. As described in Section 1.3, a screening ecotoxicity value should be equivalent to a documented and/or best conservatively estimated chronic NOAEL. Thus, for each contaminant and environmental medium, the hazard quotient can be expressed as the ratio of a potential exposure level to the NOAEL:

$$HQ = \frac{Dose}{NOAEL} \quad or \quad HQ = \frac{EEC}{NOAEL}$$

where:

HQ = hazard quotient;

Dose = estimated contaminant intake at the site (e.g., mg contaminant/kg body weight per day);

EEC = estimated environmental concentration at the site (e.g., mg contaminant/L water, mg contaminant/kg soil, mg contaminant/kg food); and

NOAEL = no-observed-adverse-effects-level (in units that match the dose or EEC).

An HQ less than one (unity) indicates that the contaminant alone is unlikely to cause adverse ecological effects. If multiple contaminants of potential ecological concern exist at the site, it might be appropriate to sum the HQs for receptors that could be simultaneously exposed to the contaminants that produce effects by the same toxic mechanism (U.S. EPA, 1986a). The sum of the HQs is called a hazard index (HI); (see Highlight 2-2). An HI less than one indicates that the group of contaminants is unlikely to cause adverse ecological effects. An HQ or HI less than one does not indicate the absence of ecological risk; rather, it should be interpreted based on the severity of the effect reported and the magnitude of the calculated quotient. As certainty in the exposure concentrations and the NOAEL increase, there is greater confidence in the predictive value of the hazard quotient model, and unity (HQ = 1) becomes a more certain pass/fail decision point.

The screening-level risk calculation is a conservative estimate to ensure that potential ecological threats are not overlooked. The calculation is used to document a decision about whether or not there is a negligible potential for ecological impacts, based on the information available at this stage. If the potential for ecological impacts exists, this calculation can be

used to eliminate the negligible-risk combinations of contaminants and exposure pathways from further consideration.

If the screening-level risk assessment indicates that adverse ecological effects are possible at environmental concentrations below standard quantitation limits, a "non detect" based on those limits cannot be used to support a "no risk" decision. Instead, the risk assessment team and risk manager should request appropriate detection limits or agree to continue to Steps 3 through 7, where exposure concentrations will be estimated from other information (e.g., fate-and-transport modeling, assumed or estimated values for non-detects).

HIGHLIGHT 2-2
Hazard Index (HI) Calculation

For contaminants that produce adverse effects by the same toxic mechanism:

$$\text{Hazard Index} = EEC_1/NOAEL_1 + EEC_2/NOAEL_2 + \ldots + EEC_i/NOAEL_i$$

where:

EEC_i = estimated environmental concentration for the i^{th} contaminant; and

$NOAEL_i$ = NOAEL for the i^{th} contaminant (expressed either as a dose or environmental concentration).

The EEC and the NOAEL are expressed in the same units and represent the same exposure period (e.g., chronic). Dose could be substituted for EEC throughout provided the NOAEL is expressed as a dose.

2.4 SCIENTIFIC/MANAGEMENT DECISION POINT (SMDP)

At the end of Step 2, the lead risk assessor communicates the results of the preliminary ecological risk assessment to the risk manager. The risk manager needs to decide whether the information available is adequate to make a risk management decision and might require technical advice from the ecological risk assessment team to reach a decision. There are only three possible decisions at this point:

(1) There is adequate information to conclude that ecological risks are negligible and therefore no need for remediation on the basis of ecological risk;

(2) The information is not adequate to make a decision at this point, and the ecological risk assessment process will continue to Step 3; or

(3) The information indicates a potential for adverse ecological effects, and a more thorough assessment is warranted.

Note that the SMDP made at the end of the screening-level risk calculation will not set a preliminary cleanup goal. Screening ecotoxicity values are derived to avoid underestimating risk. Requiring a cleanup based solely on those values would not be technically defensible.

The risk manager should document both the decision and the basis for it. If the risk characterization supports the first decision (i.e., negligible risk), the ecological risk assessment process ends here with appropriate documentation to support the decision. The documentation should include all analyses and references used in the assessment, including a discussion of the uncertainties associated with the HQ and HI estimates.

For assessments that proceed to Step 3, the screening-level analysis in Step 2 can indicate and justify which contaminants and exposure pathways can be eliminated from further assessment because they are unlikely to pose a substantive risk. (If new contaminants are discovered or contaminants are found at higher concentrations later in the site investigation, those contaminants might need to be added to the ecological risk assessment at that time.)

U.S. EPA must be confident that the SMDP made after completion of this calculation will protect the ecological components of the environment. The decision to continue beyond the screening-level risk calculation does not indicate whether remediation is necessary at the site. That decision will be made in Step 8 of the process.

2.5 SUMMARY

At the conclusion of the exposure estimate and screening-level risk calculation step, the following information should have been compiled:

(1) Exposure estimates based on conservative assumptions and maximum concentrations present; and

(2) Hazard quotients (or hazard indices) indicating which, if any, contaminants and exposure pathways might pose ecological threats.

Based on the results of the screening-level ecological risk calculation, the risk manager and lead risk assessor will determine whether or not contaminants from the site pose an ecological threat. If there are sufficient data to determine that ecological threats are negligible, the ecological risk assessment will be complete at this step with a finding of negligible ecological risk. If the data indicate that there is (or might be) a risk of adverse ecological effects, the ecological risk assessment process will continue.

Conservative assumptions have been used for each step of the screening-level ecological risk assessment. Therefore, requiring a cleanup based solely on this information would not be technically defensible. To end the assessment at this stage, the conclusion of negligible ecological risk must be adequately documented and technically defensible. A lack of information on the toxicity of a contaminant or on complete exposure pathways will result in a decision to continue with the ecological risk assessment process (Steps 3 through 7)—not

a decision to delay the ecological risk assessment until a later date when more information might be available.

STEP 3: BASELINE RISK ASSESSMENT PROBLEM FORMULATION

OVERVIEW

Step 3 of the eight-step process initiates the problem-formulation phase of the baseline ecological risk assessment. Step 3 refines the screening-level problem formulation and, with input from stakeholders and other involved parties, expands on the ecological issues that are of concern at the particular site. In the screening-level assessment, conservative assumptions were used where site-specific information was lacking. In Step 3, the results of the screening assessment and additional site-specific information are used to determine the scope and goals of the baseline ecological risk assessment. Steps 3 through 7 are required only for sites for which the screening-level assessment indicated a need for further ecological risk evaluation.

Problem formulation at Step 3 includes several activities:

- Refining preliminary contaminants of ecological concern;
- Further characterizing ecological effects of contaminants;
- Reviewing and refining information on contaminant fate and transport, complete exposure pathways, and ecosystems potentially at risk;
- Selecting assessment endpoints; and
- Developing a conceptual model with working hypotheses or questions that the site investigation will address.

At the conclusion of Step 3, there is a SMDP, which consists of agreement on four items: the assessment endpoints, the exposure pathways, the risk questions, and conceptual model integrating these components. The products of Step 3 are used to select measurement endpoints and to develop the ecological risk assessment work plan (WP) and sampling and analysis plan (SAP) for the site in Step 4. Steps 3 and 4 are, effectively, the data quality objective (DQO) process for the baseline ecological risk assessment.

3.1 THE PROBLEM-FORMULATION PROCESS

In Step 3, problem formulation establishes the goals, breadth, and focus of the baseline ecological risk assessment. It also establishes the assessment endpoints, or specific ecological values to be protected (U.S. EPA, 1992a). Through Step 3, the questions and issues that need to be addressed in the baseline ecological risk assessment are defined based on potentially complete exposure pathways and ecological effects. A conceptual model of the site is

developed that includes questions about the assessment endpoints and the relationship between exposure and effects. Step 3 culminates in an SMDP, which is agreement between the risk manager and risk assessor on the assessment endpoints, exposure pathways, and questions as portrayed in the conceptual model of the site.

The conceptual model, which is completed in Step 4, also will describe the approach, types of data, and analytical tools to be used for the analysis phase of the ecological risk assessment (Step 6). Those components of the conceptual model are formally described in the ecological risk WP and SAP in Step 4 of this eight-step process. If there is not agreement among the risk manager, lead risk assessor, and the other professionals involved with the ecological risk assessment on the initial conceptual model developed in Step 3, the final conceptual model and field study design developed in Step 4 might not resolve the issues that must be considered to manage risks effectively.

The complexity of questions developed during problem formulation does not depend on the size of a site or the magnitude of its contamination. Large areas of contamination can provoke simple questions and, conversely, small sites with numerous contaminants can require a complex series of questions and assessment endpoints. There is no rule that can be applied to gauge the effort needed for an ecological risk assessment based on site size or number of contaminants; each site should be evaluated individually.

At the beginning of Step 3, some basic information should exist for the site. At a minimum, information should be available from the site history, PA, SI, and Steps 1 and 2 of this eight-step process. For large or complex sites, information might be available from earlier site investigations.

It is important to be as complete as possible early in the process so that Steps 3 through 8 need not be repeated. Repeating the selection of assessment endpoints and/or the questions and hypotheses concerning those endpoints is appropriate only if new information indicating new threats becomes available. The SMDP process should prevent having to return to the problem formulation step because of changing opinions on the questions being asked. Repetition of Step 3 should not be confused with the intentional tiering (or phasing) of ecological site investigations at large or complex sites (see Highlight 3-1). The process of problem formulation at complex sites is the same as at more simple sites, but the number, complexity, and/or level of resolution of the questions and hypotheses can be greater at complex sites.

While problem formulation is conceptually simple, in practice it can be a complex and interactive process. Defining the ecological problems to be addressed during the baseline risk assessment involves identifying toxic mechanisms of the contaminants, characterizing potential receptors, and estimating exposure and potential ecological effects. Problem formulation also constitutes the DQO process for the baseline ecological risk assessment (U.S. EPA, 1993c,d).

The remainder of this section describes six activities to be conducted prior to the SMDP for this step: refining preliminary contaminants of ecological concern (Section 3.2); a literature search on the potential ecological effects of the contaminants (Section 3.3); qualitative evaluation of complete exposure pathways and ecosystems potentially at risk (Section 3.4); selecting assessment endpoints (Section 3.5); and developing the conceptual model and establishing risk questions (Section 3.6).

HIGHLIGHT 3-1
Tiering an Ecological Risk Assessment

Most ecological risk assessments at Superfund sites are at least a two-tier process. Steps 1 and 2 of this guidance serve as a first, or screening, tier prior to expending a larger effort for a detailed, site-specific ecological risk assessment. The baseline risk assessment may serve as the second tier. Additional tiers could be needed in the baseline risk assessment for large or complex sites where there is a need to sequentially test interdependent hypotheses developed during problem formulation (i.e., evaluating the results of one field assessment before designing a subsequent field study).

While tiering can be an effective way to manage site investigations, multiple sampling phases typically require some resampling of matrices sampled during earlier tiers and increased field-mobilization costs. Thus, in some cases, a multi-tiered ecological risk assessment might cost more than a two-tiered assessment. The benefits of tiering should be weighed against the costs.

3.2 REFINEMENT OF PRELIMINARY CONTAMINANTS OF CONCERN

The results of the screening-level risk assessment (Steps 1 and 2) should have indicated which contaminants found at the site can be eliminated from further consideration and which should be evaluated further. It is important to realize that contaminants that might pose an ecological risk can be different from those that might pose a human health risk because of differing exposure pathways, sensitivities, and responses to contaminants.

The initial list of contaminants investigated in Steps 1 and 2 included all contaminants identified or suspected to be at the site. During Steps 1 and 2, it is likely that several of the contaminants found at the site were eliminated from further assessment because the risk screen indicated that they posed a negligible ecological risk. Because of the conservative assumptions used during the risk screen, some of the contaminants retained for Step 3 might also pose negligible risk. At this stage, the risk assessor should review the assumptions used (e.g., 100 percent bioavailability) against values reported in the literature (e.g., only up to 60 percent for a particular contaminant), and consider how the HQs would change if more realistic conservative assumptions were used instead (see Section 3.4.1). For those contaminants for which the HQs drop to near or below unity, the lead risk assessor and risk manager should discuss and agree on which can be eliminated from further consideration at

this time. The reasons for dropping any contaminants from consideration at this step must be documented in the baseline risk assessment.

Sometimes, new information becomes available that indicates the initial assumptions that screened some contaminants out in Step 2 are no longer valid (e.g., site contaminant levels are higher than originally reported). In this case, contaminants can be placed back on the list of contaminants to be investigated with that justification.

Note that a contaminant should not be eliminated from the list of contaminants to be investigated only because toxicity information is lacking; instead, limited or missing toxicity information must be addressed using best professional judgment and discussed as an uncertainty.

3.3 LITERATURE SEARCH ON KNOWN ECOLOGICAL EFFECTS

The literature search conducted in Step 1 for the screening-level risk assessment might need to be expanded to obtain the information needed for the more detailed problem formulation phase of the baseline ecological risk assessment. The literature search should identify NOAELs, LOAELs, exposure-response functions, and the mechanisms of toxic responses for contaminants for which those data were not collected in Step 1. Appendix C presents a discussion of some of the factors important in conducting a literature search. Several U.S. EPA publications (e.g., U.S. EPA, 1995a,e,g,h) provide a window to original toxicity literature for contaminants often found at Superfund sites. For all retained contaminants, it is important to obtain and review the primary literature.

3.4 CONTAMINANT FATE AND TRANSPORT, ECOSYSTEMS POTENTIALLY AT RISK, AND COMPLETE EXPOSURE PATHWAYS

A preliminary identification of contaminant fate and transport, ecosystems potentially at risk, and complete exposure pathways was conducted in the screening ecological risk assessment. In Step 3, the exposure pathways and the ecosystems associated with the assessment endpoints that were retained by the screening risk assessment are evaluated in more detail. This effort typically involves compiling additional information on:

(1) The environmental fate and transport of the contaminants;

(2) The ecological setting and general flora and fauna of the site (including habitat, potential receptors, etc.); and

(3) The magnitude and extent of contamination, including its spatial and temporal variability relative to the assessment endpoints.

For individual contaminants, it is frequently possible to reduce the number of exposure pathways that need to be evaluated to one or a few "critical exposure pathways" which (1) reflect maximum exposures of receptors within the ecosystem, or (2) constitute exposure pathways to ecological receptors sensitive to the contaminant. The critical exposure pathways influence the selection of assessment endpoints for a particular site. If multiple critical exposure pathways exist, they each should be evaluated, because it is often difficult to predict which pathways could be responsible for the greatest ecological risk.

3.4.1 Contaminant Fate and Transport

Information on how the contaminants will or could be transported or transformed in the environment physically, chemically, and biologically is used to identify the exposure pathways that might lead to significant ecological effects (see Highlight 3-2). Chemically, contaminants can undergo several processes in the environment:

- Degradation,[3]
- Complexation,
- Ionization,
- Precipitation, and/or
- Adsorption.

HIGHLIGHT 3-2
Environmental Fate and Exposure

If a contaminant in an aquatic ecosystem is highly lipophilic (i.e., essentially insoluble in water), it is likely to partition primarily into sediments and not into the water column. Factors such as sediment particle size and organic carbon influence contaminant partitioning; therefore, these attributes should be characterized when sampling sediments. Similar considerations regarding partitioning should be applied to contaminants in soils.

Physically, contaminants might move through the environment by one or more means:

- Volatilization,
- Erosion,
- Deposition (contaminant sinks),
- Weathering of parent material with subsequent transport, and/or
- Water transport:
  - in solution,
  - as suspended material in the water, and
  - bulk transport of solid material.

Several biological processes also affect contaminant fate and transport in the environment:

- Bioaccumulation,
- Biodegradation,

[3] The product might be more or less toxic than the parent compound.

- Biological transformation,[4]
- Food chain transfers, and/or
- Excretion.

Additional information should be gathered on past as well as current mechanisms of contaminant release from source areas at the site. The mechanisms of release along with the chemical and physical form of a contaminant can affect its fate, transport, and potential for reaching ecological receptors.

A contaminant flow diagram (or exposure pathway diagram) comprises a large part of the conceptual model, as illustrated in Section 3.6. A contaminant flow diagram originates at the primary contaminant source(s) and identifies primary release mechanisms and contaminant transport pathways. The release and movement of the contaminants can create secondary sources (e.g., contaminated sediments in a river; see Example 3-1), and even tertiary sources.

The above information is used to evaluate where the contaminants are likely to partition in the environment, and the bioavailability of the contaminant (historically, currently, or in the future). As indicated in Section 3.2, it might be possible for the risk assessment team and the risk manager to use this information to replace some of the conservative assumptions used in the screening-level risk assessment and to eliminate additional chemicals from further evaluation at this point. Any such negotiations must be documented in the baseline risk assessment.

3.4.2 Ecosystems Potentially at Risk

The ecosystems or habitats potentially at risk depend on the ecological setting of a site. An initial source of information on the ecological setting of a site is the data collected during the preliminary site visit and characterization (Step 1), including the site ecological checklist (Appendix B). The site description should provide answers to several questions including:

- What habitats (e.g., maple-beech hardwood forest, early-successional fields) are present?
- What types of water bodies are present, if any?
- Do any other habitats listed in Exhibit 1-1 exist on or adjacent to the site?

While adequately documented information should be used, it is not critical that complete site setting information be collected during this phase of the risk assessment. However, it is important that habitats at the site are not overlooked; hence, a site visit might be needed to supplement the one conducted during the screening risk assessment. If a habitat

[4] The product might be more or less toxic than the parent compound.

EXAMPLE 3-1
Exposure Pathway Model–DDT Site

An abandoned pesticide production facility had released DDT to soils through poor handling practices during its operation. Due to erosion of contaminated soils, DDT migrated to stream sediments. The contaminated sediments represent a secondary source that might affect benthic organisms through direct contact or ingestion. Benthic organisms that have accumulated DDT can be consumed by fish, and fish that have accumulated DDT can be consumed by piscivorous birds, which are considered a valuable component of the local ecosystem. This example illustrates how contaminant transport is traced from a primary source to a secondary source and from there through a food chain to an exposure point that can affect an assessment endpoint.

actually present on the site is omitted during the problem formulation phase, this step might need to be repeated later when the habitat is found, resulting in delays and additional costs for the risk assessment.

Available information on ecological effects of contaminants (see Section 3.3) can help focus the assessment on specific ecological resources that should be evaluated more thoroughly, because some groups of organisms can be more sensitive than others to a particular contaminant. For example, a species or group of species could be physiologically sensitive to a particular contaminant (e.g., the contaminant might interfere with its vascular system); or, the species might not be able to metabolize and detoxify the particular contaminant(s) (e.g., honey bees and grass shrimp cannot effectively biodegrade PAHs, whereas fish generally can). Alternatively, an already-stressed population (e.g., due to habitat degradation) could be particularly sensitive to any added stresses.

Variation in sensitivity should not be confused with variation in exposure, which can result from behavioral and dietary differences among species. For example, predators can be exposed to higher levels of contaminants that biomagnify in food chains than herbivores. A specialist predator could feed primarily on one prey type that is a primary receptor of the contaminant. Some species might preferentially feed in a habitat where the contaminant tends to accumulate. On the other hand, a species might change its behavior to avoid contaminated areas. Both sensitivity to toxic effects of a contaminant and behaviors that affect exposure levels can influence risks for particular groups of organisms.

3.4.3 Complete Exposure Pathways

The potentially complete exposure pathways identified in Steps 1 and 2 are described in more detail in Step 3 on the basis of the refined contaminant fate and transport evaluations (Section 3.4.1) and evaluation of potential ecological receptors (Section 3.4.2).

Some of the potentially complete exposure pathways identified in Steps 1 and 2 might be ruled out from further consideration at this time. Sometimes, additional exposure pathways might be identified, particularly those originating from secondary sources. Any data gaps that result in questions about whether an exposure pathway is complete should be identified, and the type of data needed to answer those questions should be described to assist in developing the WP and SAP in Step 4.

During Step 3, the potential for food-chain exposures deserves particular attention. Some contaminants are effectively transferred through food chains, while others are not. To illustrate this point, copper and DDT are compared in Example 3-2.

EXAMPLE 3-2
Potential for Food Chain Transfer–Copper and DDT Sites

Copper can be toxic in aquatic ecosystems and to terrestrial plants. However, it is an essential nutrient for both plants and animals, and organisms can regulate internal copper concentrations within limits. For this reason, copper tends not to accumulate in most organisms or to biomagnify in food chains, and thus tends not to reach levels high enough to cause adverse responses through food chain transfer to upper-trophic-level organisms. (Copper is known to accumulate by several orders of magnitude in phytoplankton and in filter-feeding mollusks, however, and thus can pose a threat to organisms that feed on those components of aquatic ecosystems; U.S. EPA, 1985a.) In contrast, DDT, a contaminant that accumulates in fatty tissues, can biomagnify in many different types of food chains. Upper-trophic-level species (such as predatory birds), therefore, are likely to be exposed to higher levels of DDT through their prey than are lower-trophic-level species in the ecosystem.

3.5 SELECTION OF ASSESSMENT ENDPOINTS

As noted in the introduction to this guidance, an assessment endpoint is "an explicit expression of the environmental value that is to be protected" (U.S. EPA, 1992a). In human health risk assessment, only one species is evaluated, and cancer and noncancer effects are the usual assessment endpoints. Ecological risk assessment, on the other hand, involves multiple species that are likely to be exposed to differing degrees and to respond differently to the same contaminant. Nonetheless, it is not practical or possible to directly evaluate risks to all of the individual components of the ecosystem at a site. Instead, assessment endpoints focus the risk assessment on particular components of the ecosystem that could be adversely affected by contaminants from the site.

The selection of assessment endpoints includes discussion between the lead risk assessor and the risk manager concerning management policy goals and ecological values. The lead risk assessor and risk manager should seek input from the regional BTAG, PRPs, and other stakeholders associated with a site when identifying assessment endpoints for a site.

Stakeholder input at this stage will help ensure that the risk manager can readily defend the assessment endpoints when making decisions for the site. *ECO Update Volume 3, Number 1*, briefly summarizes the process of selecting assessment endpoints (U.S. EPA, 1995b).

Individual assessment endpoints usually encompass a group of species or populations with some common characteristics, such as a specific exposure route or contaminant sensitivity. Sometimes, individual assessment endpoints are limited to one species (e.g., a species known to be particularly sensitive to a site contaminant). Assessment endpoints can also encompass the typical structure and function of biological communities or ecosystems associated with a site.

Assessment endpoints for the baseline ecological risk assessment must be selected based on the ecosystems, communities, and/or species potentially present at the site. The selection of assessment endpoints depends on:

(1) The contaminants present and their concentrations;

(2) Mechanisms of toxicity of the contaminants to different groups of organisms;

(3) Ecologically relevant receptor groups that are potentially sensitive or highly exposed to the contaminant and attributes of their natural history; and

(4) Potentially complete exposure pathways.

Thus, the process of selecting assessment endpoints can be intertwined with other phases of problem formulation.

The risk assessment team must think through the contaminant mechanism(s) of ecotoxicity to determine what receptors will or could be at risk. This understanding must include how the adverse effects of the contaminants might be expressed (e.g., eggshell thinning in birds), as well as how the chemical and physical form of the contaminants influence bioavailability and the type and magnitude of adverse response (e.g., inorganic versus organic mercury).

The risk assessment team also should determine if the contaminants can adversely affect organisms in direct contact with the contaminated media (e.g., direct exposure to water, sediment, soil) or if the contaminants accumulate in food chains, resulting in adverse effects in organisms that are not directly exposed or are minimally exposed to the original contaminated media (indirect exposure). The team should decide if the risk assessment should focus on toxicity resulting from direct or indirect exposures, or if both must be evaluated.

Broad assessment endpoints (e.g., protecting aquatic communities) are generally of less value in problem formulation than specific assessment endpoints (e.g., maintaining aquatic

community composition and structure downstream of a site similar to that upstream of the site). Specific assessment endpoints define the ecological value in sufficient detail to identify the measures needed to answer specific questions or to test specific hypotheses. Example 3-3 provides three examples of assessment endpoint selection based on the hypothetical sites in Appendix A.

The formal identification of assessment endpoints is part of the SMDP for this step. Regardless of the level of effort to be expended on the subsequent phases of the risk assessment, the assessment endpoints identified are critical elements in the design of the ecological risk assessment and must be agreed upon as the focus of the risk assessment. Once assessment endpoints have been selected, testable hypotheses and measurement endpoints can be developed to determine whether or not a potential threat to the assessment endpoints exists. Testable hypotheses and measurement endpoints cannot be developed without agreement on the assessment endpoints among the risk manager, risk assessors, and other involved professionals.

3.6 THE CONCEPTUAL MODEL AND RISK QUESTIONS

The site conceptual model establishes the complete exposure pathways that will be evaluated in the ecological risk assessment and the relationship of the measurement endpoints to the assessment endpoints. In the conceptual model, the possible exposure pathways are depicted in an exposure pathway diagram and must be linked directly to the assessment endpoints identified in Section 3.5. Developing the conceptual model and risk questions are described in Sections 3.6.1 and 3.6.2, respectively. Selection of measurement endpoints, completing the conceptual model, is described in Step 4.

3.6.1 Conceptual Model

Based on the information obtained from Steps 1 and 2, knowledge of the contaminants present, the exposure pathway diagram, and the assessment endpoints, an integrated conceptual model is developed (see Example 3-4). The conceptual model includes a contaminant fate-and-transport diagram that traces the contaminants' movement from sources through the ecosystem to receptors that include the assessment endpoints (see Example 3-5). Contaminant exposure pathways that do not lead to a species or group of species associated with the proposed assessment endpoint indicate that either:

(1) There is an incomplete exposure pathway to the receptor(s) associated with the proposed assessment endpoint; or

(2) There are missing components or data necessary to demonstrate a complete exposure pathway.

EXAMPLE 3-3
Assessment Endpoint Selection–DDT, Copper, and PCB Sites

DDT Site

An assessment endpoint such as "protection of the ecosystem from the effects of DDT" would give little direction to the risk assessment. However, "protection of piscivorous birds from eggshell thinning due to DDT exposure" directs the risk assessment toward the food-chain transfer of DDT that results in eggshell thinning in a specific group of birds. This assessment endpoint provides the foundation for identifying appropriate measures of effect and exposure and ultimately the design of the site investigation. It is not necessary that a specific species of bird be identified on site. It is necessary that the exposure pathway exists and that the presence of a piscivorous bird could be expected.

Copper Site

Copper can be acutely or chronically toxic to organisms in an aquatic community through direct exposure of the organisms to copper in the water and sediments. Threats of copper toxicity to higher-trophic-level organisms are unlikely to exceed threats to organisms at the base of the food chain, because copper is an essential nutrient which is effectively regulated by most organisms if the exposure is below immediately toxic levels. Aquatic plants (particularly phytoplankton) and mollusks, however, are poor at regulating copper and might be sensitive receptors or effective in transferring copper to the next trophic level. In addition, fish fry can be very sensitive to copper in water. Based on these receptors and the potential for both acute and chronic toxicity, an appropriate general assessment endpoint for the system could be the maintenance of aquatic community composition. An operational definition of the assessment endpoint for this site would be pond fish and invertebrate community composition similar to that of other ponds of similar size and characteristics in the area.

PCB Site

The primary ecological threat of PCBs in ecosystems is not through direct exposure and acute toxicity. Instead, PCBs bioaccumulate in food chains and can diminish reproductive success in some vertebrate species. PCBs have been implicated as a cause of reduced reproductive success of piscivorous birds (e.g., cormorants, terns) in the Great Lakes (Kubiak et al., 1989; Fox et al., 1991) and of mink along several waterways (Aulerich and Ringer, 1977; Foley et al., 1988). Therefore, reduced reproductive success in high-trophic-level species exposed via their diet is a more appropriate assessment endpoint than either toxicity to organisms via direct exposure to PCBs in water, sediments, or soils, or reproductive impairment in lower-trophic-level species.

EXAMPLE 3-4
Description of the Conceptual Model–DDT Site

One of the assessment endpoints selected for the DDT site (Appendix A) is the protection of piscivorous birds. The site conceptual model includes the release of DDT from the spill areas to the adjacent stream, followed by food chain accumulation of DDT from the sediments and water through the lower trophic levels to forage fish in the stream. The forage fish are the exposure point for piscivorous birds. Eggshell thinning was selected as the measure of effect. During the literature review of the ecological effects of DDT, toxicity studies were found that reported reduced reproductive success (i.e., number of young fledged) in birds that experienced eggshell thinning of 20 percent or more (Anderson and Hickey, 1972; Dilworth et al., 1972). Based on those data, the lead risk assessor and risk manager agreed that eggshell thinning of 20 percent or more would be considered an adverse effect for piscivorous birds.

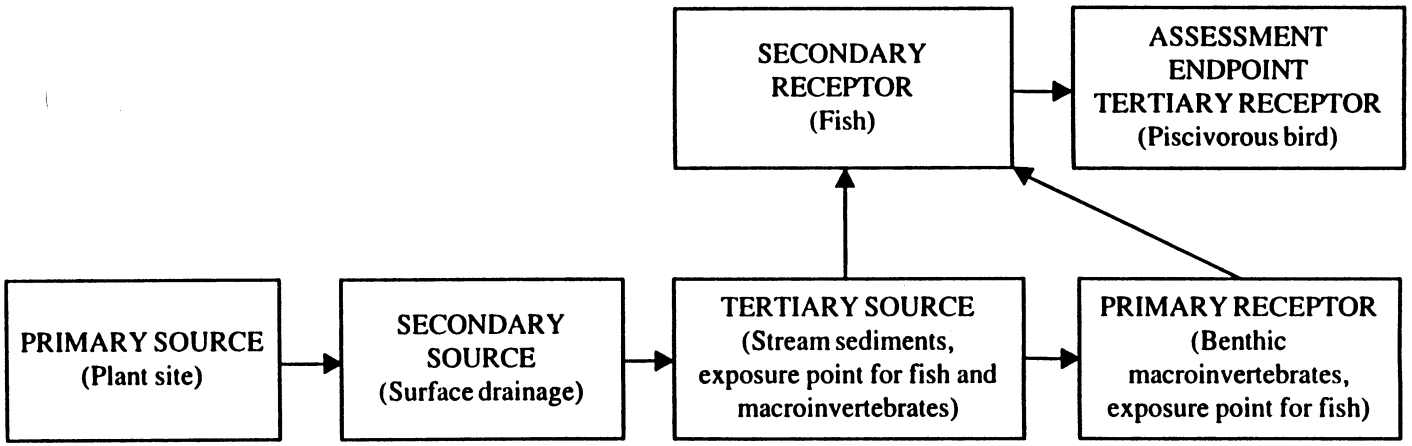
Chronic DDT exposure can also reduce some animals' ability to escape predation. Thus, DDT can indirectly increase the mortality rate of these organisms by making them more susceptible to predators (Cooke, 1971; Krebs et al., 1974). That effect of DDT on prey also can have an indirect consequence for the predators. If predators are more likely to capture the more contaminated prey, the predators could be exposed to DDT at levels higher than represented in the average prey population.

If case (1) is true, the proposed assessment endpoint should be reevaluated to determine if it is an appropriate endpoint for the site. If case (2) is true, then additional field data could be needed to evaluate contaminant fate and transport at the site. Failure to identify a complete exposure pathway that does exist at the site can result in incorrect conclusions or in extra time and effort being expended on a supplementary investigation.

As indicated in Section 3.5, appropriate assessment endpoints differ from site to site, and can be at one or more levels of biological organization. At any particular site, the appropriate assessment endpoints might involve local populations of a particular species, community-level integrity, and/or habitat preservation. The site conceptual model must encompass the level of biological organization appropriate for the assessment endpoints for the site. The conceptual model can use assumptions that generally represent a group of organisms or ecosystem components.

The intent of the conceptual model is not to describe a particular species or site exactly as much as it is to be systematic, representative, and conservative where information is lacking (with assumptions biased to be more likely to overestimate than to underestimate risk). For example, it is not necessary or even recommended to develop new test protocols to use species that exist at a site to test the toxicity of site media (See Step 4). Species used in standardized laboratory toxicity tests (e.g., fathead minnows, *Hyallela* amphipods) usually are adequate surrogates for species in their general taxa and habitat at the site.

EXAMPLE 3-5
Conceptual Model Diagram–DDT Site



3.6.2 Risk Questions

Ecological risk questions for the baseline risk assessment at Superfund sites are basically questions about the relationships among assessment endpoints and their predicted responses when exposed to contaminants. The risk questions should be based on the assessment endpoints and provide a basis for developing the study design (Step 4) and for evaluating the results of the site investigation in the analysis phase (Step 6) and during risk characterization (Step 7).

HIGHLIGHT 3-3
Definitions:
Null and Test Hypotheses

Null hypothesis: Usually a hypothesis of no differences between two populations formulated for the express purpose of being rejected.

Test (or alternative) hypothesis: An operational statement of the investigator's research hypothesis.

When appropriate, formal hypothesis testing is preferred to make explicit what error rates are acceptable and what magnitude of effect is considered biologically important. However, it might not be practical for many assessment endpoints or be the only acceptable way to state questions about those endpoints. See Example 4-1 in the next chapter.

The most basic question applicable to virtually all Superfund sites is whether site-related contaminants are causing or have the potential to cause adverse effects on the assessment endpoint(s). To use the baseline ecological risk assessment in the FS to evaluate remedial alternatives, it is helpful if the specific contaminant(s) responsible can be identified. Thus refined, the question becomes "does (or could) chemical X cause adverse effects on the assessment endpoint?" In general, there are four lines of evidence that can be used to answer this question:

(1) Comparing estimated or measured exposure levels to chemical X with levels that are known from the literature to be toxic to receptors associated with the assessment endpoints;

(2) Comparing laboratory bioassays with media from the site and bioassays with media from a reference site;

(3) Comparing *in situ* toxicity tests at the site with *in situ* toxicity tests in a reference body of water; and

(4) Comparing observed effects in the receptors associated with the site with similar receptors at a reference site.

These lines of evidence are considered further in Step 4, as measurement endpoints are selected to complete the conceptual model and the site-specific study is designed.

3.7 SCIENTIFIC/MANAGEMENT DECISION POINT (SMDP)

At the conclusion of Step 3, there is a SMDP. The SMDP consists of agreement on four items: contaminants of concern, assessment endpoints, exposure pathways, and risk questions. Those items can be summarized with the assistance of the diagram of the conceptual model. Without agreement between the risk manager, risk assessors, and other involved professionals on the conceptual model to this point, measurement endpoints cannot be selected, and a site study cannot be developed effectively. Example 3-5 shows the conceptual model for the DDT site example in Appendix A.

3.8 SUMMARY

By combining information on: (1) the potential contaminants present; (2) the ecotoxicity of the contaminants; (3) environmental fate and transport; (4) the ecological setting; and (5) complete exposure pathways, an evaluation is made of what aspects of the ecosystem at the site could be at risk and what the adverse ecological response could be. "Critical exposure pathways" are based on: (1) exposure pathways to sensitive species' populations or communities; and (2) exposure levels associated with predominant fate and transport mechanisms at a site.

Based on that information, the risk assessors and risk manager agree on assessment endpoints and specific questions or testable hypotheses that, together with the rest of the conceptual model, form the basis for the site investigation. At this stage, site-specific information on exposure pathways and/or the presence of specific species is likely to be incomplete. By using the conceptual model developed thus far, measurement endpoints can be selected, and a plan for filling information gaps can be developed and written into the ecological WP and SAP as described in Step 4.

STEP 4: STUDY DESIGN AND DATA QUALITY OBJECTIVE PROCESS

OVERVIEW

The site conceptual model begun in Step 3, which includes assessment endpoints, exposure pathways, and risk questions or hypotheses, is completed in Step 4 with the development of measurement endpoints. The conceptual model then is used to develop the study design and data quality objectives. The products of Step 4 are the ecological risk assessment WP and SAP, which describe the details of the site investigation as well as the data analysis methods and data quality objectives (DQOs). As part of the DQO process, the SAP specifies acceptable levels of decision errors that will be used as the basis for establishing the quantity and quality of data needed to support ecological risk management decisions.

The lead risk assessor and the risk manager should agree that the WP and SAP describe a study that will provide the risk manager with the information needed to fulfill the requirements of the baseline risk assessment and to incorporate ecological considerations into the site remedial process. Once this step is completed, most of the professional judgment needed for the ecological risk assessment will have been incorporated into the design and details of the WP and SAP. This does not limit the need for qualified professionals in the implementation of the investigation, data acquisition, or data interpretation. However, there should be no fundamental changes in goals or approach to the ecological risk assessment once the WP and SAP are finalized.

It is important to coordinate this step with the WP and SAP for the site investigation, which is used to document the nature and extent of contamination and to evaluate human health risks.

Step 4 of the ecological risk assessment establishes the measurement endpoints (Section 4.1), completing the conceptual model begun in Step 3. Step 4 also establishes the study design (Section 4.2) and data quality objectives based on statistical considerations (Section 4.3) for the site assessment that will accompany site-specific studies for the remedial investigation. The site conceptual model is used to identify which points or assumptions in the risk assessment include the greatest degree of conservatism or uncertainty. The field sampling then can be designed to address the risk model parameters that have important effects on the risk estimates (e.g., bioavailability and toxicity of contaminants in the field, contaminant concentrations at exposure points).

The products of Step 4 are the WP and SAP for the ecological component of the field investigations (Section 4.4). Involvement of the BTAG in the preparation, review, and approval of WPs and SAPs can help ensure that the ecological risk assessment is well focused, performed efficiently, and technically correct.

The WP and SAP should specify the site conceptual model developed in Step 3, and the measurement endpoints developed in the beginning of Step 4. The WP describes:

- Assessment endpoints;
- Exposure pathways;
- Questions and testable hypotheses;
- Measurement endpoints and their relation to assessment endpoints; and
- Uncertainties and assumptions.

The SAP should describe:

- Data needs;
- Scientifically valid and sufficient study design and data analysis procedures;
- Study methodology and protocols, including sampling techniques;
- Data reduction and interpretation techniques, including statistical analyses; and
- Quality assurance procedures and quality control techniques.

The SAP must include the data reduction and interpretation techniques, because it is necessary to known how the data will be interpreted to specify the number of samples needed.

Prior to formal agreement on the WP and SAP, the proposed field sampling plan is verified in Step 5.

4.1 ESTABLISHING MEASUREMENT ENDPOINTS

As indicated in the Introduction, a measurement endpoint is defined as "a measurable ecological characteristic that is related to the valued characteristic chosen as the assessment endpoint" and is a measure of biological effects (e.g., mortality, reproduction, growth) (U.S. EPA, 1992a; although this definition may change—see U.S. EPA 1996a). Measurement endpoints are frequently numerical expressions of observations (e.g., toxicity test results, community diversity measures) that can be compared statistically to a control or reference site to detect adverse responses to a site contaminant. As used in this guidance, measurement endpoints can include measures of exposure (e.g., contaminant concentrations in water) as well as measures of effect. The relationship between measurement and assessment endpoints must be clearly described within the conceptual model and must be based on scientific evidence. This is critical because the assessment and measurement endpoints usually are different endpoints (see the Introduction and Highlight 4-1).

Typically, the number of measurement endpoints that are potentially appropriate for any given assessment endpoint and circumstance is limited. The most appropriate measurement endpoints for an assessment endpoint depend on several considerations, a primary one being how many and which lines of evidence are needed to support risk-management decisions at the site (see Section 3.6.2). Given the potential ramifications of site actions, the site risk manager might want to use more than one line of evidence to identify site-specific thresholds for effects. The risk manager and risk assessors must consider the utility of each type of data given the cost of collecting those data and the likely sensitivity of the risk estimates to the data.

HIGHLIGHT 4-1
Importance of Distinguishing Measurement from Assessment Endpoints

If a measurement endpoint is mistaken for an assessment endpoint, the misperception can arise that Superfund is basing a remediation on an arbitrary or esoteric justification. For example, protection of a few invertebrate and algal species could be mistaken as the basis for a remedial decision, when the actual basis for the decision is the protection of the aquatic community as a whole (including higher-trophic-level game fish that depend on lower trophic levels in the community), as indicated by a few sensitive invertebrate and algal species.

There are some situations in which it might only be necessary or possible to compare estimated or measured contaminant exposure levels at a site to ecotoxicity values derived from the literature. For example, for contaminants in surface waters for which there are state water-quality standards, exceedance of the standards indicates that remediation to reduce contaminant concentrations in surface waters to below these levels could be needed whether impacts are occurring or not. For assessment endpoints for which impacts are difficult to demonstrate in the field (e.g., because of high natural variability), and toxicity tests are not possible (e.g., food-chain accumulation is involved), comparing environmental concentrations with a well-supported ecotoxicity value might have to suffice.

A bioassay using contaminated media from the site can suffice if the risk manager and risk assessor agree that laboratory tests with surrogate species will be taken as indicative of likely effects on the assessment endpoint. For sites with complex mixtures of contaminants without robust ecotoxicity values and high natural variability in potential measures for the assessment endpoint, either laboratory or *in situ* toxicity testing might be the best technique for evaluating risks to the assessment endpoint. For inorganic substances in soils or sediments, bioassays often are needed to determine the degree to which a contaminant is bioavailable at a particular site. Laboratory toxicity tests can indicate the potential for adverse impacts in the field, while *in situ* toxicity testing with resident organisms can provide evidence of actual impacts occurring in the field.

Sometimes more than one line of evidence is needed to reasonably demonstrate that contaminants from a site are likely to cause adverse effects on the assessment endpoint. For

example, total recoverable copper in a surface water body to which a water quality standard did not apply could exceed aquatic ecotoxicity values, but not cause adverse effects because the copper is only partially bioavailable or because the ecotoxicity value is too conservative for the particular ecosystem. Additional evidence from bioassays or community surveys could help resolve whether the copper is actually causing adverse effects (See Example 4-1). Alternatively, if stream community surveys indicate impairment of community structure downstream of a site, comparing contaminant concentrations with aquatic toxicity values can help identify which contaminants are most likely to be causing the effect. When some lines of evidence conflict with others, professional judgment is needed to determine which data should be considered more reliable or relevant to the questions.

EXAMPLE 4-1
Lines of Evidence–Copper Site

Primary question: Are ambient copper levels in sediments causing adverse effects in benthic organisms in the pond?

Possible lines of evidence phrased as test hypotheses:

(1) Mortality in early life stages of benthic aquatic insects in contact with sediments from the site significantly exceeds mortality in the same kinds of organisms in contact with sediments from a reference site (e.g., $p \leq 0.1$).

(2) Mortality in *in situ* toxicity tests in sediments at the pond significantly exceeds mortality in *in situ* toxicity tests in sediments at a reference pond (e.g., $p \leq 0.1$).

(3) There are significantly fewer numbers of benthic aquatic insect species present per m^2 of sediment at the pond near the seep than at the opposite side of the pond (e.g., $p \leq 0.1$).

Statistical and biological significance: Differences in the incidence of adverse effects between groups of organisms exposed to contaminants from the site and groups not exposed might be statistically significant, but not biologically important, depending on the endpoint and the power of the statistical test. Natural systems can sustain some level of perturbation without changing in structure or function. The risk assessor needs to evaluate what level of effect will be considered biologically important. Given the limited power of small sample sizes to detect an effect, the risk assessor might decide that any difference that is statistically detectable at a p level of 0.1 or less is important biologically.

Once there is agreement on which lines of evidence are required to answer questions concerning the assessment endpoint, the measurement endpoints by which the questions or test hypotheses will be examined can be selected.

Each measurement endpoint should represent the same exposure pathway and toxic mechanism of action as the assessment endpoint it represents; otherwise, irrelevant exposure pathways or toxic mechanisms might be evaluated. For example, if a contaminant primarily causes damage to vertebrate kidneys, the use of daphnids (which do not have kidneys) would be inappropriate.

Potential measurement endpoints in toxicity tests or in field studies should be evaluated according to how well they can answer questions about the assessment endpoint or support or refute the hypotheses developed for the conceptual model. Statistical considerations, including sample size and statistical power described in Section 4.3, also must be considered in selecting the measurement endpoints. The following subsections describe additional considerations for selecting measurement endpoints, including species/community/habitat (Section 4.1.1), relationship to the contaminant(s) of concern (Section 4.1.2), and mechanisms of ecotoxicity (Section 4.1.3).

4.1.1 Species/Community/Habitat Considerations

The function of a measurement endpoint is to represent an assessment endpoint for the site. The measurement endpoint must allow clear inferences about potential changes in the assessment endpoint. Whenever assessment and measurement endpoints are not the same (which usually is the case), measurement endpoints should be selected to be inclusive of risks to all of the species, populations, or groups included in the assessment endpoint that are not directly measured. In other words, the measurement endpoint should be representative of the assessment endpoint for the site and not lead to an underestimate of risk to the assessment endpoint. Example 4-2 illustrates this point for the DDT site in Appendix A.

In selecting a measurement endpoint, the species and life stage, population, or community chosen should be the one(s) most susceptible to the contaminant for the assessment endpoint in question. For species and populations, this selection is based on a review of the species: (1) life history; (2) habitat utilization; (3) behavioral characteristics; and (4) physiological parameters. Selection of measurement endpoints also should be based on which routes of exposure are likely. For communities, careful evaluation of the contaminant fate and transport in the environment is essential.

4.1.2 Relationship of the Measurement Endpoints to the Contaminant of Concern

Additional criteria to consider when selecting measurement endpoints are inherent properties (such as the physiology or behavioral characteristics of the species) or life history parameters that make a species useful in evaluating the effects of site-specific contaminants.

HIGHLIGHT 4-2
Terminology and Definitions

In the field of ecotoxicology, there historically have been multiple definitions for some terms, including definitions for direct effects, indirect effects, acute effects, chronic effects, acute tests, and chronic tests. This multiplicity of definitions has resulted in misunderstandings and inaccurate communication of study designs. Definitions of these and other terms, as they are used in this document, are provided in the glossary. When consulting other reference materials, the user should evaluate how the authors defined terms.

For example, *Chironomus tentans* (a species of midge that is used as a standard sediment toxicity testing species in the larval stage) is considered more tolerant of metals contamination than is *C. riparius*, a similar species (Klemm et al., 1990; Nebeker et al., 1984; Pascoe et al., 1989). To assess the effects of exposure of benthic communities to metal-contaminated sediment, *C. riparius* might be the better species to use as a test organism for many aquatic systems to ensure that risks are not underestimated. In general, the most sensitive of the measurement endpoints appropriate for inferring risks to the assessment endpoint should be used. If all else is equal, however, species that are commonly used in the laboratory are preferred over non-standard laboratory species to improve test precision.

Some species have been identified as being particularly sensitive to certain contaminants. For example, numerous studies have demonstrated that mink are among the most sensitive of the tested mammalian species to the toxic effects of PCBs (U.S. EPA, 1995a). Species that rely on quick reactions or behavioral responses to avoid predators can be particularly sensitive to contaminants affecting the central nervous system, such as mercury. Thus, the sensitivity of the measurement endpoint relative to the assessment endpoint should be considered for each contaminant of concern.

EXAMPLE 4-2
Selecting Measurement Endpoints–DDT Site

As described in Example 3-1, one of the assessment endpoints selected for the DDT site is the protection of piscivorous birds from egg-shell thinning due to DDT exposure. The belted kingfisher was selected as a piscivorous bird with the smallest home range that could utilize the area of the site, thereby maximizing the calculated dose to a receptor. In this illustration, the kingfishers are used as the most highly exposed of the piscivorous birds potentially present. Thus, one can conclude that, if the risk assessment shows no threat of eggshell thinning to the kingfisher, there should be minimal or no threat to other piscivorous birds that might utilize the site. Thus, eggshell thinning in belted kingfishers is an appropriate measurement endpoint for this site.

4.1.3 Mechanisms of Ecoxicity

A contaminant can exert adverse ecological effects in many ways. First, a contaminant might affect an organism after exposure for a short period of time (acute) or after exposure over an extended period of time (chronic). Second, the effect of a contaminant could be lethal (killing the organism) or sublethal (causing adverse effects other than death, such as reduced growth, behavioral changes, etc.). Sublethal effects can reduce an organism's lifespan or reproductive success. For example, if a contaminant reduces the reaction speed of a prey species, the prey can become more susceptible to predation. Third, a contaminant might act directly or indirectly on an organism. Direct effects include lethal or sublethal effects of the chemical on the organism. Indirect effects occur when the contaminant damages the food, habitat, predator-prey relationships, or competition of the organism in its community.

Mechanisms of ecotoxicity and exposure pathways have already been considered during problem formulation and identification of the assessment endpoints. However, toxicity issues are revisited when selecting appropriate measurement endpoints to ensure that they measure the assessment endpoint's toxic response of concern.

4.2 STUDY DESIGN

In Section 4.1, one or more lines of evidence that could be used to answer questions or to test hypotheses concerning the assessment endpoint(s) were identified. This section provides recommendations on how to design a field study for: bioaccumulation and field tissue residue studies (Section 4.2.1); population/community evaluations (Section 4.2.2); and toxicity testing (Section 4.2.3). A thorough understanding of the strengths and limitations of these types of field studies is necessary to properly design any investigation.

Typically, no one line of evidence can stand on its own. Analytic chemistry on co-located samples and other lines of evidence are needed to support a conclusion. When population/community evaluations are coupled with toxicity testing and media chemistry, the procedure often is referred to as a triad approach (Chapman et al., 1992; Long and Chapman, 1985). This method has proven effective in defining the area affected by contaminants in sediments of several large bays and estuaries.

The development of exposure-response relationships is critical for evaluating risk management options; thus, for all three types of studies, sampling is applied to a contamination gradient when possible as well as compared to reference data. Reference data are baseline values or characteristics that should represent the site in the absence of contaminants released from the site. Reference data might be data collected from the site before contamination occurred or new data collected from a reference site. The reference site can be the least impacted (or unimpacted) area of the Superfund site or a nearby site that is

ecologically similar, but not affected by the site's contaminants. For additional information on selecting and using reference information in Superfund ecological risk assessments, see *ECO Update Volume 2, Number 1* (U.S. EPA, 1994e).

The following subsections present a starting point for selecting an appropriate study design for the different types of biological sampling that might apply to the site investigation.

4.2.1 Bioaccumulation and Field Tissue Residue Studies

Bioaccumulation and field tissue residue studies typically are conducted at sites where contaminants are likely to accumulate in food chains. The studies help to evaluate contaminant exposure levels associated with measures of effect for assessment endpoint species.

The degree to which a contaminant is transferred through a food chain can be evaluated in several ways. The most common type of study reported in the literature is a contaminant bioaccumulation (uptake) study. As indicated in Section 2.2.1, the most conservative BAF values identified in the literature generally are used to estimate bioaccumulation in Step 2 of the screening-level risk assessment. Where the potential for overestimating bioaccumulation by using conservative literature values to represent the site is substantial, additional evaluation of the literature for values more likely to apply to the site or a site-specific tissue residue study might be advisable.

A tissue residue study generally is conducted on organisms that are in the exposure pathway (i.e., food chain) associated with the assessment endpoint. Data seldom are available to link tissue residue levels in the sampled organisms to adverse effects in those organisms. Literature toxicity studies usually associate effects with an administered dose (or data that can be converted to an administered dose), not a tissue residue level. Thus, the purpose of a field tissue residue study usually is to measure contaminant concentrations in foods consumed by the species associated with the assessment endpoint. This measurement minimizes the uncertainty associated with estimating a dose (or intake) to that species, particularly in situations in which several media and trophic levels are in the exposure pathway.

The concentration of a contaminant in the primary prey/food also should be linked to an exposure concentration from a contaminated medium (e.g., soil, sediment, water), because it is the medium, not the food chain, that will be remediated. Thus, contaminant concentrations must be measured in environmental media at the same locations at which the organisms are collected along contaminant gradients and at reference locations. Co-located samples of the contaminated medium and organisms are needed to establish a correlation between the tissue residue levels and contamination levels in the medium under evaluation; these studies are most effective if conducted over a gradient of contaminant concentrations. In addition, tissue residues from sessile organisms (e.g., rooted plants, clams) are easier to attribute to specific contaminated areas than are tissue residues from mobile organisms (e.g.,

large fish). Example 4-3 illustrates these concepts using the DDT site example in Appendix A.

EXAMPLE 4-3
Tissue Residue Studies–DDT Site

In the DDT site example, a forage fish (e.g., creek chub) will be collected at several locations with known DDT concentrations in sediments. The forage fish will be analyzed for body burdens of DDT, and the relationship between the DDT levels in the sediments and the levels in the forage fish will be established. The forage fish DDT concentrations can be used to evaluate the DDT threat to piscivorous birds feeding on the forage fish at each location. Using the DDT concentrations measured in fish that correspond to a LOAEL and NOAEL for adverse effects in birds and the relationship between the DDT levels in the sediments and in the forage fish, the corresponding sediment contamination levels can be estimated. Those sediment DDT concentrations can then be used to estimate a cleanup level that would reduce threats of eggshell thinning to piscivorous birds.

Although it might seem obvious, it is important to confirm that the organisms examined for tissue residue levels are in the exposure pathways of concern established by the conceptual model. Food items targeted for collection should be those that are likely to constitute a large portion of the diet of the species of concern (e.g., new growth on maple trees, rather than cattails, as a food source for deer) and/or represent pathways of maximum exposure. If not, erroneous conclusions or study delays and added costs can result. Because specific organisms often can only be captured in one season, the timing of the study can be critical, and failure to plan accordingly can result in serious site management difficulties.

There are numerous factors that must be considered when selecting a species in which to measure contaminant residue levels. Several investigators have discussed the "ideal" characteristics of the species to be collected and analyzed. The recommendations of Phillips (1977, 1978) include that the species selected should be:

(1) Able to accumulate the chemical of concern without being adversely affected by the levels encountered at the site;

(2) Sedentary (small home range) in order to be representative of the area of collection;

(3) Abundant in the study area; and

(4) Of reasonable size to give adequate tissue for analysis (e.g., 10 grams for organic analysis and 0.5 gram for metal analysis for many laboratories (Roy F. Weston, Inc., 1994)).

Additional considerations for some situations would be that the species is:

(5) Sufficiently long-lived to allow for sampling more than one age class; and

(6) Easy to sample and hardy enough to survive in the laboratory (allowing for the organisms to eliminate contaminants from their gastrointestinal tract prior to analysis, if desired, and allowing for laboratory studies on the uptake of the contaminant).

It is usually not possible or necessary to find an organism that fulfills all of the above requirements. The selection of an organism for tissue analysis should balance these characteristics with the hypotheses being tested, knowledge of the contaminants' fate and transport, and the practicality of using the particular species. In the following sections, several of the factors mentioned above are described in greater detail.

Ability to accumulate the contaminant. The objectives of a tissue residue study are (1) to measure bioavailability directly; (2) to provide site-specific estimates of exposure to higher-trophic-level organisms; and (3) to relate tissue residue levels to concentrations in environmental media (e.g., in soil, sediment, or water). Sometimes these studies also can be used to link tissue residue levels with observed effects in the organisms sampled. However, in a "pure" accumulation study, the species selected for collection and tissue analysis should be ones that can accumulate a contaminant(s) without being adversely affected by the levels encountered in the environment. While it is difficult to evaluate whether or not a population in the field is affected by accumulation of a contaminant, it is important to try. Exposure that results in adverse responses might alter the animal's feeding rates or efficiency, diet, degree of activity, or metabolic rate, and thereby influence the animal's daily intake or accumulation of the contaminant and the estimated BAF. For example, if the rate of bioaccumulation of a contaminant in an organism decreases with increasing environmental concentrations (e.g., its toxic effects reduce food consumption rates), using a BAF determined at low environmental concentrations to estimate bioaccumulation at high environmental concentrations would overestimate risk. Conversely, if bioaccumulation increased with increasing environmental concentrations (e.g., its toxic effects impair the organisms' ability to excrete the contaminant), using a BAF determined at low environmental concentrations would underestimate risks at higher environmental concentrations.

Consideration of the physiology and biochemistry of the species selected for residue analysis also is important. Some species can metabolize certain organic contaminant(s) (e.g., fish can metabolize PAHs). If several different types of prey are consumed by a species of concern, it would be more appropriate to analyze prey species that do not metabolize the contaminant.

Home range. When selecting species for residue analyses, one should be confident that the contaminant levels found in the organism depend on the contaminant levels in the environmental media under evaluation. Otherwise, valid conclusions cannot be drawn about ecological risks posed by contaminants at the site. The home range, particularly the foraging areas within the home range, and movement patterns of a species are important in making this determination. Organisms do not utilize the environment uniformly. For species that have large home ranges or are migratory, it can be difficult to evaluate potential exposure to contaminants at the site. Attribution of contaminant levels in an organism to contaminant levels in the surrounding environment is easiest for animals with small home and foraging ranges and limited movement patterns. Examples of organisms with small home ranges include young-of-the-year fish, burrowing crustacea (such as fiddler crabs or some crayfish), and small mammals.

Species also should be selected for residue analysis to maximize the overlap between the area of contamination and the species' home range or feeding range. This provides a conservative evaluation of potential exposure levels. The possibility that a species' preferred foraging areas within a home range overlap the areas of maximum contamination also should be considered.

Population size. A species selected for tissue residue analysis should be sufficiently abundant at the site that adequate numbers (and sizes) of individuals can be collected to support the tissue mass requirements for chemical analysis and to achieve the sample size needed for statistical comparisons. The organisms actually collected should be not only of the same species, but also of similar age or size to reduce data variability when BAFs are being evaluated. The practicality of using a particular species is evaluated in Step 5.

Size/composites. When selecting species in which to measure tissue residue levels, it is best to have individual animals large enough for chemical analysis, without having to pool (combine) individuals prior to chemical analysis. However, composite samples will be needed if individuals from the species selected cannot yield sufficient tissue for the required analytical methods. Linking contaminant levels in organisms to concentrations in environmental media is easier if composites are made up of members of the same species, sex, size, and age, and therefore exhibit similar accumulation characteristics. When deciding whether or not to pool samples, it is important to consider what impact the loss of information on variability of contaminant levels along these dimensions will have on data interpretation. The size, age, and sex of the species collected should be representative of the range of prey consumed by the species of concern.

Summary. Although it can be difficult to meet all of the suggested criteria for selecting a species for tissue residue studies, an attempt should be made to meet as many criteria as possible. No formula is available for ranking the factors in order of importance within a particular site investigation because the ranking depends on the study objectives. However, a key criterion is that the organism be sedentary or have a limited home range. It is difficult to connect site contamination to organisms that migrate over great distances or that

have extremely large home ranges. Further information on factors that can influence bioaccumulation is available from the literature (e.g., Phillips, 1977, 1978; U.S. EPA, 1995d).

4.2.2 Population/Community Evaluations

Population/community evaluations, or biological field surveys, are potentially useful for both contaminants that are toxic to organisms through direct exposure to the contaminated medium and contaminants that bioaccumulate in food chains. In either case, careful consideration must be given to the mechanism of contaminant effects. Since population/community evaluations are "impact" evaluations, they typically are not predictive. The release of the contaminant must already have occurred and exerted an effect in order for the population/community evaluation to be an effective tool for a risk assessment.

Population and community surveys evaluate the current status of an ecosystem, often using several measures of population or community structure (e.g., standing biomass, species richness) or function (e.g., feeding group analysis). The most commonly used measures include number of species and abundance of organisms in an ecosystem, although some species are difficult to evaluate. It is difficult to detect changes in top predator populations affected by bioaccumulation of substances in their food chain due to the mobility of top predators. Some species, most notably insects, can develop a tolerance to contaminants (particularly pesticides); in these cases, a population/community survey would be ineffective for evaluating existing impacts. While population/community evaluations can be useful, the risk assessors should consider the level of effort required as well as the difficulty in accounting for natural variability.

A variety of population/community evaluations have been used at Superfund sites. Benthic macroinvertebrate surveys are the most commonly conducted population/community evaluations. There are methods manuals (e.g., U.S. EPA 1989c, 1990a) and publications that describe the technical procedures for conducting these studies. In certain instances, fish community evaluations have proven useful at Superfund sites. However, these investigations typically are more labor-intensive and costly than a comparable macroinvertebrate study. In addition, fish generally are not sensitive measures of the effects of sediment contamination, because they usually are more mobile than benthic macroinvertebrates. Terrestrial plant community evaluations have been used to a limited extent at Superfund sites. For those surveys, it is important to include information about historical land use and physical habitat disruption in the uncertainty analysis.

Additional information on designing field studies and on field study methods can be found in *ECO Update Volume 2, Number 3* (U.S. EPA, 1994d).

Although population- and community-level studies can be valuable, several factors can confound the interpretation of the results. For example, many fish and small mammal populations normally cycle in relation to population density, food availability, and other factors. Vole populations have been known to reach thousands of individuals per acre and

then to decline to as low as tens of individuals per acre the following years without an identifiable external stressor (Geller, 1979). It is important that the "noise of the system" be evaluated so that the impacts attributed to chemical contamination at the site are not actually the result of different, "natural" factors. Populations located relatively close to each other can be affected independently: one might undergo a crash, while another is peaking. Physical characteristics of a site can isolate populations so that one population level is not a good indicator of another; for example, a paved highway can be as effective a barrier as a river, and populations on either side can fluctuate independently. Failure to evaluate such issues can result in erroneous conclusions. The level of effort required to resolve some of these issues can make population/community evaluations impractical in some circumstances.

4.2.3 Toxicity Testing

The bioavailability and toxicity of site contaminants can be tested directly with toxicity tests. As with other methods, it is critical that the media tested are in exposure pathways relevant to the assessment endpoint. If the site conceptual model involves exposure of benthic invertebrates to contaminated sediments, then a solid-phase toxicity test using contaminated sediments (as opposed to a water-column exposure test) and an infaunal species would be appropriate. As indicated earlier, the species tested and the responses measured must be compatible with the mechanism of toxicity. Some common site contaminants are not toxic to most organisms at the same environmental concentrations that threaten top predators because the contaminant biomagnifies in food chains (e.g., PCBs); toxicity tests using contaminated media from the site would not be appropriate for evaluating this type of ecological threat.

There are numerous U.S. EPA methods manuals and ASTM guides and procedures for conducting toxicity tests (see references in the Bibliography). While documented methods exist for a wide variety of toxicity tests, particularly laboratory tests, the risk assessor must evaluate what a particular toxicity test measures and, just as importantly, what it does not measure. Questions to consider when selecting an appropriate toxicity test include:

(1) What is the mechanism of toxicity of the contaminant(s)?

(2) What contaminated media are being evaluated (water, soil, sediment)?

(3) What toxicity test species are available to test the media being evaluated?

(4) What life stage of the species should be tested?

(5) What should the duration of the toxicity test be?

(6) Should the test organisms be fed during the test?

(7) What endpoints should be measured?

There are a limited number of toxicity tests that are readily available for testing environmental media. Many of the aquatic toxicity tests were developed for the regulation of aqueous discharges to surface waters. These tests are useful, but one must consider the original purpose of the test.

New toxicity tests are being developed continually and can be of value in designing a Superfund site ecological risk assessment. However, when non-standard tests are used, complete documentation of the specific test procedures is necessary to support use of the data.

In situ toxicity tests involve placing organisms in locations that might be affected by site contaminants and in reference locations. Non-native species should not be used, because of the risk of their release into the environment in which they could adversely affect (e.g., prey on or outcompete) resident species. *In situ* tests might provide more realistic evidence of existing adverse effects than laboratory toxicity tests; however, the investigator has little control over many environmental parameters and the experimental organisms can be lost to adverse weather or other events (e.g., human interference) at the site or reference location.

For additional information on using toxicity tests in ecological risk assessments, see *ECO Update Volume 2, Numbers 1* and *2* (U.S. EPA, 1994b,c).

4.3 DATA QUALITY OBJECTIVES AND STATISTICAL CONSIDERATIONS

The SAP indicates the number and location of samples to be taken, the number of replicates for each sampling location, and the method for determining sampling locations. In specifying those parameters, the investigator needs to consider, among other things, the DQOs and statistical methods that will be used to analyze the data.

4.3.1 Data Quality Objectives

The DQO process represents a series of planning steps that can be employed throughout the development of the WP and SAP to ensure that the type, quantity, and quality of environmental data to be collected during the ecological investigation are adequate to support the intended application. Problem formulation in Steps 3 and 4 is essentially the DQO process. By employing problem formulation and the DQO process, the investigator is able to define data requirements and error levels that are acceptable for the investigation prior to the collection of data. This approach helps ensure that results are appropriate and defensible for decision making. The specific goals of the general DQO process are to:

- Clarify the study objective and define the most appropriate types of data to collect;

- Determine the most appropriate field conditions under which to collect the data; and

- Specify acceptable levels of decision errors that will be used as the basis for establishing the quantity and quality of data needed to support risk management decisions.

As the discussion of Steps 3 and 4 indicates, those goals are subsumed in the problem formulation phase of an ecological risk assessment. Several U.S. EPA publications provide detailed descriptions of the DQO process (U.S. EPA, 1993c,d,f, 1994f). Because many of the steps of the DQO process are already covered during problem formulation, the DQO process should be reviewed by the investigator and applied as needed.

4.3.2 Statistical Considerations

Sampling locations can be selected "randomly" to characterize an area or non-randomly, as along a contaminant concentration gradient. The way in which sampling locations are selected determines which statistical tests, if any, are appropriate for evaluating test hypotheses.

If a toxicity test is to be used to identify contaminant concentrations in the environment associated with a threshold for adverse effects, the statistical power of the test is important. The threshold for effects is assumed to be between the NOAEL and LOAEL of a toxicity test (see Section 7.3.1). For toxicity tests that use a small number of test and control organisms or for which the toxic response is highly variable, the increase in response rate of the test animals compared with controls often must be relatively high (e.g., 30 to 50 percent increase) for the response to be considered a LOAEL (i.e., statistically increased level of an adverse response compared with control levels). If a NOAEL-to-LOAEL range that might represent a 20 to 50 percent increase in adverse effect is unacceptable (e.g., a population is unlikely to sustain itself with an additional 40 percent mortality), then the power of the study design must be increased, usually by increasing sample size, but sometimes by taking full advantage of all available information to improve the power of the design (e.g., stratified sampling, special tests for trends, etc.). A limitation on the use of toxicity values from the literature is that often, the investigator does not discuss the statistical power of the study design, and hence does not indicate the minimum statistically detectable effect level. Appendix D describes additional statistical considerations, including a description of Type I and Type II error, statistical power, statistical models, and power efficiency.

In evaluating the results of statistical analyses, one should remember that a statistically significant difference relative to a control or reference population does not necessarily imply a biologically important or ecologically significant difference (see Example 4-1).

4.4 CONTENTS OF WORK PLAN AND SAMPLING AND ANALYSIS PLAN

The WP and SAP for the ecological investigation should be developed as part of the initial RI sampling event if possible. If not, the WP and SAP can be developed as an

additional phase of the site investigation. In either case, the format of the WP and SAP should be similar to that described by U.S. EPA (1988a, 1989b). Accordingly, those documents should be consulted when developing the ecological investigation WP and SAP.

The WP and SAP are typically written as separate documents. In that case, the WP can be submitted for the risk manager's review so that any concerns with the approach can be resolved prior to the development of the SAP. For some smaller sites, it might be more practical to combine the two documents, in which case, the investigators should discuss the overall objectives and approach with the risk manager to ensure that all parties agree.

The WP and SAP are briefly described in Sections 4.4.1 and 4.4.2, respectively. A plan for testing the SAP before the site WP and SAP are signed and the investigation begins is described in Section 4.4.3.

4.4.1 Work Plan

The purpose of the WP is to document the decisions and evaluations made during problem formulation and to identify additional investigative tasks needed to complete the evaluation of risks to ecological resources. As presented in U.S. EPA (1988a), the WP generally includes the following:

- A general overview and background of the site including the site's physical setting, ecology, and previous uses;
- A summary and analysis of previous site investigations and conclusions;
- A site conceptual model, including an identification of the potential exposure pathways selected for analysis, the assessment endpoints and questions or testable hypotheses, and the measurement endpoints selected for analysis;
- The identification of additional site investigations needed to conduct the ecological risk assessment; and
- A description of assumptions used and the major sources of uncertainty in the site conceptual model and existing information.

The general scope of the additional sampling activities also is presented in the WP. A detailed description of the additional sampling activities is presented in the SAP along with an anticipated schedule of the site activities.

4.4.2 Sampling and Analysis Plan

The SAP typically consists of two components: a field sampling plan (FSP) and a quality assurance project plan (QAPP). The FSP provides guidance for all field work by

providing a detailed description of the sampling and data-gathering procedures to be used for the project. The QAPP provides a description of the steps required to achieve the objectives dictated by the intended use of the data.

Field sampling plan. The FSP provides a detailed description of the samples needed to meet the objectives and scope of the investigation outlined in the WP. The FSP for the ecological assessment should be detailed enough that a sampling team unfamiliar with the site would be able to gather all the samples and/or required field data based on the guidelines presented in the document. The FSP for the ecological investigation should include a description of the following elements:

- Sampling type and objectives;
- Sampling location, timing, and frequency;
- Sample designation;
- Sampling equipment and procedures; and
- Sample handling and analysis.

A detailed description of those elements for chemical analyses is provided in Appendix B of U.S. EPA (1988a). Similar specifications should be developed for the biological sampling.

Quality assurance project plan. The objective of the QAPP is to provide a description of the policy, organization, functional activities, and quality control protocols necessary for achieving the study objectives. Highlight 4-3 presents the elements typically contained in a QAPP.

U.S. EPA has prepared guidance on the contents of a QAPP (U.S. EPA, 1987a, 1988a, 1989a). Formal quality assurance and quality control (QA/QC) procedures exist for some types of ecological assessments, for example, for laboratory toxicity tests on aquatic species. For standardized laboratory tests, there are formal QA/QC procedures that specify (1) sampling and handling of hazardous wastes; (2) sources and culturing of test organisms; (3) use of reference toxicants, controls, and exposure replicates; (4) instrument calibration; (5) record keeping; and (6) data evaluation. For other types of ecological assessments, however, QA/QC procedures are less well defined (e.g., for biosurveys of vegetation, terrestrial vertebrates). BTAG

HIGHLIGHT 4-3
Elements of a QAPP

(1) Project description
(2) Designation of QA/QC responsibilities
(3) Statistical tests and data quality objectives
(4) Sample collection and chain of custody
(5) Sample analysis
(6) System controls and preventive maintenance
(7) Record keeping
(8) Audits
(9) Corrective actions
(10) Quality control reports

members can provide input on appropriate QA/QC procedures based on their experience with Superfund sites.

4.4.3 Field Verification of Sampling Plan and Contingency Plans

For biological sampling, uncontrolled variables can influence the availability of species to be sampled, the efficiency of different types of sampling techniques, and the level of effort required to achieve the sample sizes specified in the SAP. As a consequence, the risk assessor should develop a plan to test the sampling design before the WP and SAP are signed and the site investigation begins. Otherwise, field sampling during the site investigation could fail to meet the DQOs specified in the SAP, and the study could fail to meet its objectives. Step 5 provides a description of the field verification of the sampling design.

To the extent that potential field problems can be anticipated, contingency plans also should be specified in the SAP. An example of a contingency plan is provided in Steps 5 and 6 (Examples 5-2 and 6-1).

4.5 SCIENTIFIC/MANAGEMENT DECISION POINT (SMDP)

The completion of the ecological risk assessment WP and SAP should coincide with an SMDP. Within this SMDP, the ecological risk assessor and the ecological risk manager agree on: (1) selection of measurement endpoints; (2) selection of the site investigation methods; and (3) selection of data reduction and interpretation techniques. The WP or SAP also should specify how inferences will be drawn from the measurement to the assessment endpoints.

4.6 SUMMARY

At the conclusion of Step 4, there will be an agreement on the contents of the WP and SAP. As noted earlier, these plans can be parts of a larger WP and SAP that are developed to meet other remedial investigation needs, or they can be separate documents. When possible, any field sampling efforts for the ecological risk assessment should overlap with other site data collection efforts to reduce sampling costs and to prevent redundant sampling.

The WP and/or the SAP should specify the methods by which the collected data will be analyzed. The plan(s) should include all food-chain-exposure-model parameters, data reduction techniques, data interpretation methods, and statistical analyses that will be used.

STEP 5: FIELD VERIFICATION OF SAMPLING DESIGN

OVERVIEW

Before the WP and SAP are signed, it is important to verify that the field sampling plan they specify is appropriate and implementable at the site. If this has not already been done, it should be done now. During field verification of the sampling design, the testable hypotheses, exposure pathway models, and measurement endpoints are evaluated for their appropriateness and implementability. The assessment endpoint(s), however, should not be under evaluation in this step; the appropriateness of the assessment endpoint should have been resolved in Step 3. If an assessment endpoint is changed at this step, the risk assessor must return to Step 3, because the entire process leading to the actual site investigation in Step 6 assumes the selection of appropriate assessment endpoints.

5.1 PURPOSE

The primary purpose of field verification of the sampling plan is to ensure that the samples specified by the SAP actually can be collected. A species that will be associated with a measurement endpoint and/or exposure point concentration should have been observed at the preliminary site characterization or noted during previous site visits. During this step, previously obtained information should be verified and the feasibility of sampling will need to be checked by a site visit. Preliminary sampling will determine if the targeted species is present and—equally important—collectable in sufficient numbers or total biomass to meet data quality objectives. This preliminary field assessment also allows for final confirmation of the habitats that exist on or near the site. Habitat maps are verified a final time, and interpretations of aerial photographs can be checked.

Final decisions on reference areas also should be made in this step. The reference areas should be chosen to be as similar as possible to the site in all aspects except contamination. Parameters to be evaluated for similarity include, but are not limited to: slope, habitat, species potentially present, soil and sediment characteristics, and for surface waters, flow rates, substrate type, water depth, temperature, turbidity, oxygen levels, water hardness, pH, and other standard water quality parameters. If several on-site habitats or habitat variables are being investigated, then several reference areas could be required. Reference areas should be as free of site-related contaminants above background levels as practical.

5.2 DETERMINING SAMPLING FEASIBILITY

When sampling biota, it is difficult to predict what level of effort will be necessary to obtain an adequate number of individuals of the required size. Some preliminary field measurements often can help determine adequate sampling efforts to attain the sample sizes specified in the SAP for statistical analyses. The WP and SAP should be signed and the site investigation should be implemented immediately after verification of the sampling design to limit effects of uncontrolled field variables. For example, evaluation of current small mammal population density might indicate to the investigator that 400 trap-nights instead of 50 are necessary to collect the required number of small mammals. If there is a time lag between the field sampling verification and the actual site investigation, it could be necessary to reverify the field sampling to determine if conditions have changed.

Sampling methods for abiotic media also should be tested. There is a wide variety of sampling devices and methods, and it is important to use the most appropriate, as the following examples illustrate:

- When sampling a stream's surface water, if the stream is only three inches deep, collecting the water directly into 32-ounce bottles would not be practical.

- Sampling the substrate in a stream might be desirable, but if the substrate is bedrock, it might not be feasible or the intent of the sampling design.

An exposure-response relationship between contamination and biological effects is a key component of establishing causality during the analysis phase of the baseline risk assessment (Step 6). If extent-of-contamination sampling is conducted in phases, abiotic exposure media and biotic samples must be collected simultaneously because the interactions (both temporal and spatial) between the matrix to be remediated and the biota are crucial to the development of a field exposure-response relationship. Failure to collect one sample properly or to coordinate samples temporally can significantly impact the interpretation of the data.

Sampling locations need to be checked to make sure that they are appropriately described and placed within the context of the sampling plan. Directions for a sediment sample "to be taken 5 feet from the north side of stream A," could cause confusion if the stream is only 4 feet wide, or if the sampler doesn't know if the sample should be taken in the stream, or 5 feet away from the edge of the stream. All samples should be checked against the intended use of the data to be obtained.

All pathways for the migration of contaminants off site should be evaluated, such as windblown dust, surface water runoff, and erosion. Along these pathways, a gradient of decreasing contamination with increasing distance from the site might exist. Site-specific ecological evaluations and risk assessments can be more useful to risk managers if gradients of contamination can be located and evaluated.

Contaminant migration pathways might have changed, either due to natural causes (e.g., storms) or site remediation activities (e.g., erosion channels might have been filled or dug up to prevent further migration of contaminants). Channels of small or large streams, brooks, or rivers might have moved; sites might have been flooded. All of the assumptions of the migration and exposure pathways need to be verified prior to the full site investigation. If a contaminant gradient is necessary for the sampling plan, it is important to verify that the gradient exists and that the range of contaminant concentrations is appropriate. A gradient of contamination that causes no impacts at the highest concentration measured has as little value as a gradient that kills everything at the lowest concentration measured; in either case, the gradient would not provide useful exposure-response information. A gradient verification requires chemical sampling, but field screening-level analyses might be effective.

These and other problems associated with the practical implementation of sampling should be resolved prior to finalizing the SAP to the extent practicable. Assessing the feasibility of the sampling plan before the site investigation begins saves costs in the long term because it minimizes the chances of failing to meet DQOs during the site investigation.

Examples 5-1 and 5-2 describe the field verification of the sampling plan for the hypothetical copper and DDT sites illustrated in Appendix A. Note that the scope of the field verification differs for the copper and DDT sites. For the DDT site, a modification to the study design was necessary. For both sites, the issues were resolved and a sign-off was obtained at the SMDP for this step.

Any change in measurement endpoints will require that exposure pathways to the new measurement endpoint be checked. The new measurement endpoint must fit into the established conceptual model. Changes to measurement endpoints might require revision of the conceptual model and agreement to the changes at the SMDP. It is highly desirable that the agreed-upon conceptual model should be modified and approved by the same basic group of individuals who developed it.

5.3 SCIENTIFIC/MANAGEMENT DECISION POINT (SMDP)

The SMDP for the field verification of the sampling design is the signing of the finalized WP and SAP. Any changes to the investigation proposed in Step 4 must be made with agreement from the risk manager and risk assessment team. The risk manager must understand what changes have been made and why, and must ensure that the risk management decisions can be made from the information that the new study design can provide. The risk assessors must be involved to ensure that the assessment endpoints and testable hypotheses are still being addressed.

In the worst cases, changes in the measurement endpoints could be necessary, with corresponding changes to the risk hypotheses and sampling design. Any new measurement endpoints must be evaluated according to their utility for inferring changes in the assessment

EXAMPLE 5-1
Field Verification of Sampling Design–Copper Site

Copper was released from a seep area of a landfill adjacent to a small pond; the release and resulting elevated copper levels in the pond are of concern. The problem formulation and conceptual model stated that the assessment endpoint was the maintenance of a typical pond community for the area, including the benthic invertebrates and fish. Toxicity testing was selected to evaluate the potential toxicity of copper to aquatic organisms. Three toxicity tests were selected: a 10-day solid-phase sediment toxicity test (with the amphipod *Hyalella azteca*), and two water column tests (i.e., the 7-day growth test with the green alga *Selenastrum capricornutum* and the fathead minnow, *Pimephales promelas*, 7-day larval growth test). The study design specified that sediment and water for the toxicity tests would be collected at the leachate seeps known to be at the pond edge, and at three additional equidistant locations transecting the pond (including the point of maximum pond depth). The pond contains water year-round; however, the seep flow depends on rainfall. Therefore, it is only necessary to verify that the leachate seep is active at the time of sampling.

endpoints and their compatibility with the site conceptual model (from Steps 3 and 4). Loss of the relationship between measurement endpoints and the assessment endpoints, the risk questions or testable hypothesis, and the site conceptual model will result in a failure to meet study objectives.

Despite one's best efforts to conduct a sound site assessment, unexpected circumstances might still make it necessary for the sampling plan to be changed in the field. Any changes should be agreed to and documented by the lead risk assessor in consultation with the risk manager.

Once the finalized WP and SAP are approved and signed, Step 6 should begin.

5.4 SUMMARY

In summary, field verification of the sampling plan is very important to ensuring that the DQOs of the site investigation can be met. This step verifies that the selected assessment endpoints, testable hypotheses, exposure pathway model, measurement endpoints, and study design from Steps 3 and 4 are appropriate and implementable at the site. By verifying the field sampling plan prior to conducting the full site investigation, well-considered alterations can be made to the study design and/or implementation if necessary. These changes will ensure that the ecological risk assessment meets the study objectives.

If changing conditions force changes to the sampling plan in the field (e.g., selection of a different reference site), the changes should be agreed to and documented by the lead risk assessor in consultation with the risk manager.

EXAMPLE 5-2
Field Verification of Sampling Design–DDT Site

For the stream DDT site, the assessment endpoint was protection of piscivorous birds from adverse reproductive effects. The conceptual model included the exposure pathway of sediment to forage fish to the kingfisher. The measurement endpoint selected was tissue residue levels in creek chub (*Semotilus atromaculatus*), which could be associated with contaminant levels in sediments. Existing information on the stream contamination indicates that a gradient of contamination exists and that five specific sampling locations should be sufficient to characterize the gradient to the point where concentrations are unlikely to have adverse effects. The study design specified that 10 creek chub of the same size and sex be collected at each location. Each chub should be approximately 20 grams, so that minimum sample mass requirements could be met without using composite samples for analysis. In addition, QA/QC protocol requires that 10 more fish be collected at one of the locations.

In this example, a site assessment was necessary to verify that a sufficient number of creek chub of the specified size would be present to meet the sampling requirements. Stream conditions were evaluated to determine what fish sampling technique would work at the targeted locations. A field assessment was conducted, and several fish collection techniques were used to determine which was the most effective for the site. Collected creek chub and other fish were examined to determine the size range available and whether the sex of the individuals could be determined.

The site assessment indicated that the creek chub might not be present in sufficient numbers to provide the necessary biomass for chemical analyses. Based upon those findings, a contingency plan was agreed to, which stated that both the creek chub and the longnosed dace (*Rhinichthys cataractae*) would be collected. If the creek chub were collected at all locations in sufficient numbers, then those samples would be analyzed and the dace would be released. If sufficient creek chub could not be collected but sufficient longnosed dace could, the longnosed dace would be analyzed and the creek chub released. If neither species could be collected at all locations in sufficient numbers, then a mix of the two species would be used; however, for any given sampling location only one species would be used to make the sample. In addition, at one location, which preferably had high DDT levels in the sediment, sufficient numbers (20 grams) of both species would be collected to allow comparison (and calibration) of the accumulation between the two species.

STEP 6: SITE INVESTIGATION AND ANALYSIS PHASE

OVERVIEW

Information collected during the site investigation is used to characterize exposures and ecological effects. The site investigation includes all of the field sampling and surveys that are conducted as part of the ecological risk assessment. The site investigation and analysis of exposure and effects should be straightforward, following the WP and SAP developed in Step 4 and tested in Step 5.

Exposure characterization relies heavily on data from the site investigation and can involve fate-and-transport modeling. Much of the information for characterizing potential ecological effects was gathered from the literature review during problem formulation, but the site investigation might provide evidence of existing ecological impacts and additional exposure-response information.

6.1 INTRODUCTION

The site investigation (Section 6.2) and analysis phase (Section 6.3) of the ecological risk assessment should be straightforward. In Step 4, all issues related to the study design, sample collection, DQOs, and procedures for data reduction and interpretation should have been identified and resolved. However, as described in Step 5, there are circumstances that can arise during a site investigation that could require modifications to the original study design. If any unforeseen events do require a change to the WP or SAP, all changes must be agreed upon at the SMDP (Section 6.4). The results of Step 6 are used to characterize ecological risks in Step 7.

6.2 SITE INVESTIGATION

The WP for the site investigation is based on the site conceptual model and should specify the assessment endpoints, risk questions, and testable hypotheses. The SAP for the site investigation should specify the relationship between measurement and assessment endpoints, the necessary number, volume, and types of samples to be collected, and the sampling techniques to be used. The SAP also should specify the data reduction and interpretation techniques and the DQOs. The feasibility of the sampling design was tested in Step 5. Therefore, the site investigation should be a direct implementation of the previously designed study.

During the site investigation, it is important to adhere to the DQOs and to any requirements for co-located sampling. Failure to collect one sample properly or to coordinate samples temporally can significantly affect interpretation of the data. Changing field conditions (Section 6.2.1) and new information on the nature and extent of contamination (Section 6.2.2) can require a change in the SAP.

6.2.1 Changing Field Conditions

In instances where unexpected conditions arise in the field that make the collection of specified samples impractical or not ideal, the ecological risk assessor should reevaluate the feasibility of the sampling design as described in Step 5. Field efforts should not necessarily be halted, but decisions to change sampling procedures or design must be agreed to by the risk manager and lead risk assessor or project-delegated equivalents.

Field modifications to study designs are not uncommon during field investigations. When the WP and SAP provide a precise conceptual model and study design with specified data analyses, informed modifications to the SAP can be made to comply with the objectives of the study. As indicated in Step 4, contingency plans can be included in the original SAP in anticipation of situations that might arise during the site investigation (see Example 6-1). Any modifications, and the reasons for the modifications, must be documented in the baseline risk assessment.

EXAMPLE 6-1
Fish Sampling Contingency Plan–DDT Site

At the DDT site where creek chub are to be collected for DDT tissue residue analyses, a contingency plan for the site investigation was developed. An alternate species, the longnosed dace, was specified with the expectation that, at one or all locations, the creek chub might be absent at the time of the site investigation. Such contingency plans are prudent even when the verification of the field sampling design described in Step 5 indicates that the samples are obtainable.

6.2.2 Unexpected Nature or Extent of Contamination

It is not uncommon for an initial sampling phase of the RI to reveal that contamination at levels of concern extend beyond areas initially established for characterizing contamination and ecological effects at the site or that contaminant gradients are much steeper than anticipated. If this contingency changes the opportunity for evaluating biological effects along a contamination gradient, the ecological risk assessors and risk manager need to determine whether additional sampling (e.g., further downstream from the site) is needed.

Thus, it is important for the ecological risk assessors to track information on the nature and extent of contamination as RI sampling is conducted.

On occasion, new contaminants are identified during an RI. In this case, the risk assessors and site manager will need to return to Step 1 to screen the new contaminants for ecological risk.

Immediate analysis of the data for each type of sampling and communication between the risk assessors and risk managers can help ensure that the site investigation is adequate to achieve the study goals and objectives when field modifications are necessary. If a change to the WP or SAP is needed, the lead risk assessor and risk manager must agree on all changes (the SMDP in Section 6.4).

6.3 ANALYSIS OF ECOLOGICAL EXPOSURES AND EFFECTS

The analysis phase of the ecological risk assessment consists of the technical evaluation of data on existing and potential exposures (Section 6.3.1) and ecological effects (Section 6.3.2) at the site. The analysis is based on the information collected during Steps 1 through 5 and often includes additional assumptions or models to interpret the data in the context of the site conceptual model. As illustrated in Exhibit 6-1, analysis of exposure and effects is performed interactively, with the analysis of one informing the analysis of the other. This step follows the data interpretation and analysis methods specified in the WP and SAP, and therefore should be a straightforward process.

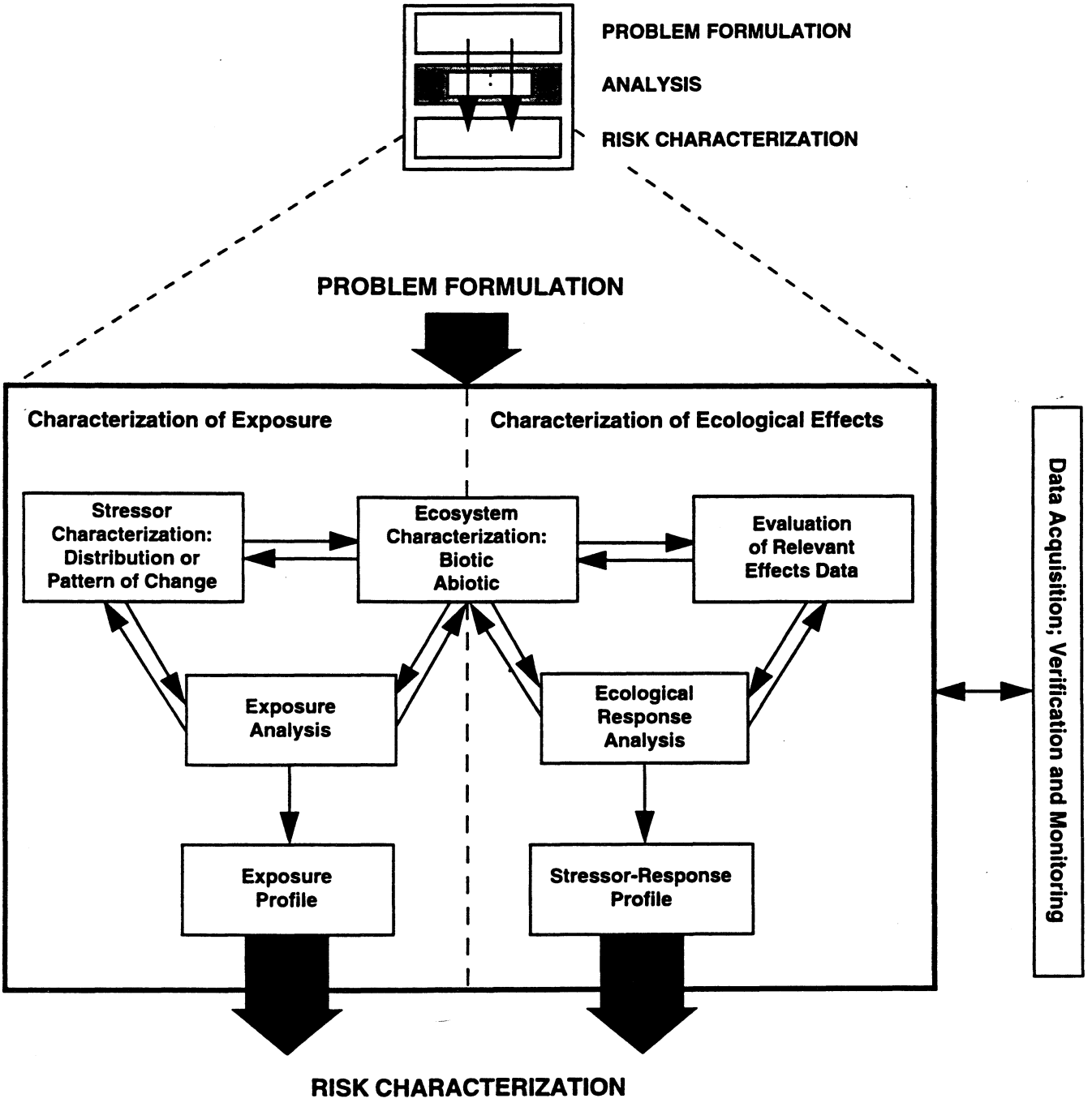
In the analysis phase, the site-specific data obtained during the site investigation replace many of the assumptions that were made for the screening-level analysis in Steps 1 and 2. For the exposure and ecological effects characterizations, the uncertainties associated with the field measurements and with assumptions where site-specific data are not available must be documented.

6.3.1 Characterizing Exposures

Exposure can be expressed as the co-occurrence or contact of the stressor with the ecological components, both in time and space (U.S. EPA, 1992a). Thus, both the stressor and the ecosystem must be characterized on similar temporal and spatial scales. The result of the exposure analysis is an exposure profile that quantifies the magnitude and spatial and temporal patterns of exposure as they relate to the assessment endpoints and risk questions developed during problem formulation. The exposure profile and a description of associated uncertainties and assumptions serve as input to the risk characterization in Step 7.

Stressor characterization involves determining the stressor's distribution and pattern of change. The analytic approach for characterizing ecological exposures should have been established in the WP and SAP on the basis of the site conceptual model. For chemical

EXHIBIT 6-1
Analysis Phase (U.S. EPA, 1992a)



stressors at Superfund sites, usually a combination of fate-and-transport modeling and sampling data from the site are used to predict the current and likely future nature and extent of contamination at a site.

When characterizing exposures, the ecological context of the site established during problem formulation is analyzed further, both to understand potential effects of the ecosystem on fate and transport of chemicals in the environment and to evaluate site-specific characteristics of species or communities of concern. Any site-specific information that can be used to replace assumptions based on information from the literature or from other sites is incorporated into the description of the ecological components of the site. Remaining assumptions and uncertainties in the exposure model (Highlight 6-1) should be documented.

HIGHLIGHT 6-1
Uncertainty in Exposure Models

The accuracy of an exposure model depends on the accuracy of the input parameter values and the validity of the model's structure (i.e., the degree to which it represents the actual relationships among parameters at the site). Field measurements can be used to calibrate model outputs or intermediate calculations. Such field measurements should be specified in the WP and SAP. For example, studies of tissue residue levels often are used to calibrate exposure and food-chain models.

6.3.2 Characterizing Ecological Effects

At this point, all evidence for existing and potential adverse effects on the assessment endpoints is analyzed. The information from the literature review on ecological effects is integrated with any evidence of existing impacts based on the site investigation (e.g., toxicity testing). The methods for analyzing site-specific data should have been specified in the WP and SAP, and thus should be straightforward. Both exposure-response information and evidence that site contaminants are causing or can cause adverse effects are evaluated.

Exposure-response analysis. The exposure-response analysis for a Superfund site describes the relationship between the magnitude, frequency, or duration of a contaminant stressor in an experimental or observational setting and the magnitude of response. In this phase of the analysis, measurement endpoints are related to the assessment endpoints using the logical structure provided by the conceptual model. Any extrapolations that are required to relate measurement to assessment endpoints (e.g., between species, between response levels, from laboratory to field) are explained. Finally, an exposure-response relationship is described to the extent possible (e.g., by a regression equation), including the confidence limits (quantitative or qualitative) associated with the relationship.

Under some circumstances, site-specific exposure-response information can be obtained by evaluating existing ecological impacts along a contamination gradient at the site. Statistical techniques to identify or describe the relationship between exposure and response from the field data should have been specified in the WP and SAP. The potential for

confounding stressors that might correlate with the contamination gradient should be documented (e.g., decreasing water temperature downstream of a site; reduced soil erosion further from a site).

An exposure-response analysis is of particular importance to risk managers who must balance human health and ecological concerns against the feasibility and effectiveness of remedial options. An exposure-response function can help a risk manager to specify the trade-off between the degree of cleanup and likely benefits of the cleanup and to balance ecological and financial costs and benefits of different remedial options, as discussed in Step 8.

When exposure-response data are not available or cannot be developed, a threshold for adverse effects can be developed instead, as in Step 2. For the baseline risk assessment, however, site-specific information should be used instead of conservative assumptions whenever possible.

Evidence of causality. At Superfund sites, evidence of causality is key to the risk assessment. Thus, it is important to evaluate the strength of the causal association between site-related contaminants and effects on the measurement and assessment endpoints. Demonstrating a correlation between a contaminant gradient and ecological impacts at a site is a key component of establishing causality, but other evidence can be used in the absence of such a demonstration. Moreover, an exposure-response correlation at a site is not sufficient to demonstrate causality, but requires one or more types of supporting evidence and analysis of potential confounding factors. Hill's (1965) criteria for evaluating causal associations are outlined in the *Framework* (U.S. EPA, 1992a).

6.4 SCIENTIFIC/MANAGEMENT DECISION POINT (SMDP)

An SMDP during the site investigation and analysis phase is needed only if alterations to the WP or SAP become necessary. In the worst case, changes in measurement endpoints could be required, with corresponding changes to the testable hypotheses and sampling design. Any new measurement endpoints must be evaluated according to their utility for inferring changes in the assessment endpoints and their compatibility with the site conceptual model; otherwise, the study could fail to meet its objectives.

Proposed changes to the SAP must be made in consultation with the risk manager and the risk assessors. The risk manager must understand what changes have been made and why, and must ensure that the risk management decisions can be made from the information that the new study design can provide. The risk assessors must be involved to ensure that the assessment endpoints and study questions or testable hypotheses are still being addressed.

6.5 SUMMARY

The site investigation step of the ecological risk assessment should be a straightforward implementation of the study designed in Step 4 and verified in Step 5. In instances where unexpected conditions arise in the field that indicate a need to change the study design, the ecological risk assessors should reevaluate the feasibility or adequacy of the sampling design. Any proposed changes to the WP or SAP must be agreed upon by both the risk assessment team and the risk manager and must be documented in the baseline risk assessment.

The analysis phase of the ecological risk assessment consists of the technical evaluation of data on existing and potential exposures and ecological effects and is based on the information collected during Steps 1 through 5 and the site investigation in Step 6. Analyses of exposure and effects are performed interactively, and follow the data interpretation and analysis methods specified in the WP and SAP. Site-specific data obtained during Step 6 replace many of the assumptions that were made for the screening-level analysis in Steps 1 and 2. Evidence of an exposure-response relationship between contamination and ecological responses at a site helps to establish causality. The results of Step 6 are used to characterize ecological risks in Step 7.

STEP 7: RISK CHARACTERIZATION

OVERVIEW

In risk characterization, data on exposure and effects are integrated into a statement about risk to the assessment endpoints established during problem formulation. A weight-of-evidence approach is used to interpret the implications of different studies or tests for the assessment endpoints. In a well-designed study, risk characterization should be straightforward, because the procedures were established in the WP and SAP. The risk characterization section of the baseline ecological risk assessment should include a qualitative and quantitative presentation of the risk results and associated uncertainties.

7.1 INTRODUCTION

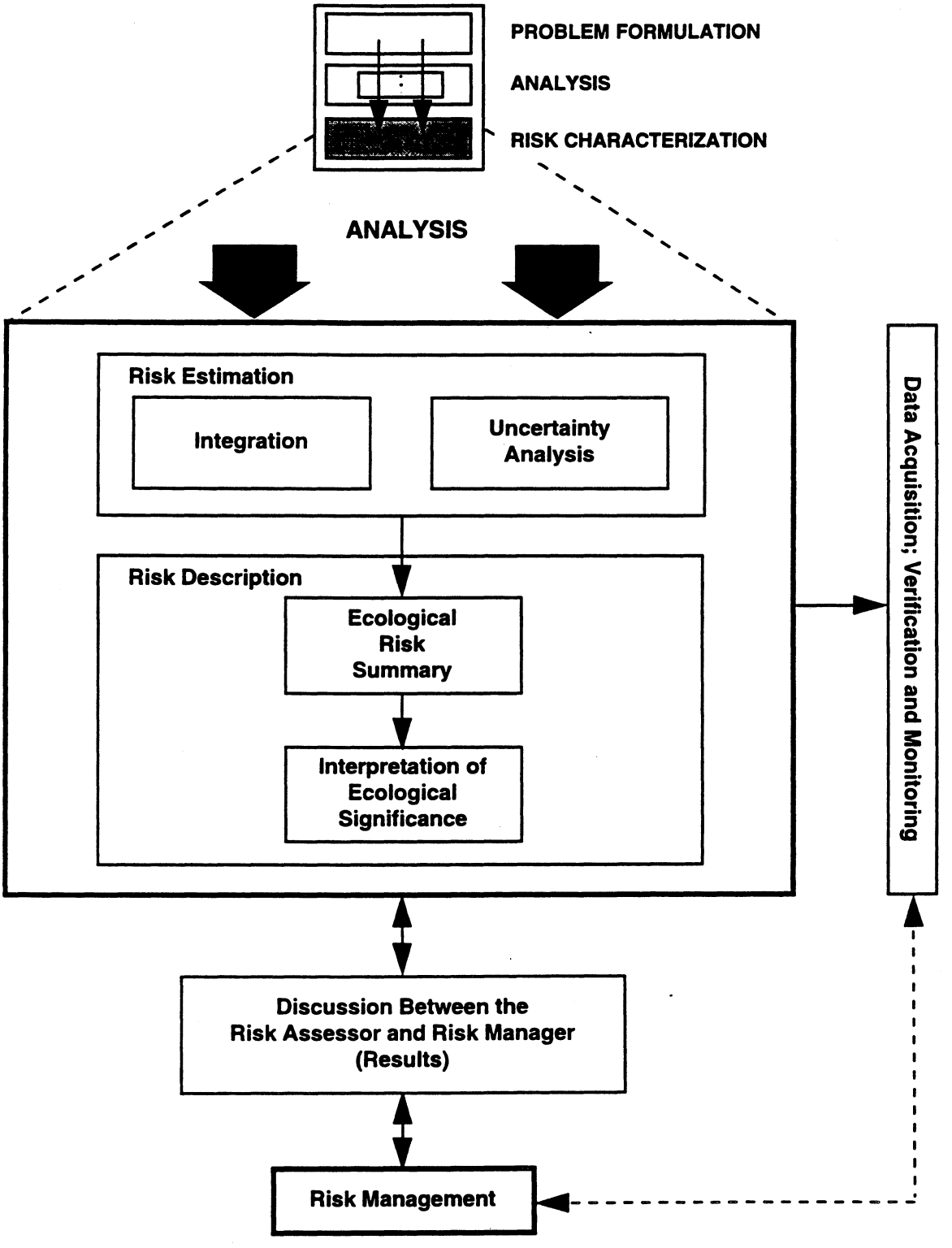
Risk characterization is the final phase of the risk assessment process and includes two major components: risk estimation and risk description (U.S. EPA, 1992a; Exhibit 7-1). Risk estimation (Section 7.2) consists of integrating the exposure profiles with the exposure-effects information and summarizing the associated uncertainties. The risk description (Section 7.3) provides information important for interpreting the risk results and, in the Superfund Program, identifies a threshold for adverse effects on the assessment endpoints (Section 7.4).

It is U.S. EPA policy that risk characterization should be consistent with the values of "transparency, clarity, consistency, and reasonableness" (U.S. EPA, 1995f). "Well-balanced risk characterizations present risk conclusions and information regarding the strengths and limitations of the assessment for other risk assessors, EPA decision-makers, and the public" (U.S. EPA, 1995f). Thus, when preparing the risk characterization, the risk assessment team should make sure that the documentation of risks is easy to follow and understand, with all assumptions, defaults, uncertainties, professional judgments, and any other inputs to the risk estimate clearly identified and easy to find.

7.2 RISK ESTIMATION

Documentation of the risk estimates should describe how inferences are made from the measurement endpoints to the assessment endpoints established in problem formulation. As stated earlier, it is not the purpose of this document to provide a detailed guidance on the selection and utilization of risk models. The risk assessment team should have developed and the risk manager should have agreed upon the conceptual model used to characterize risk, its

EXHIBIT 7-1
Risk Characterization (U.S. EPA, 1992a)



assumptions, uncertainties, and interpretation in Steps 3 through 5. This agreement is specified in the site WP and SAP and is the purpose of the SMDPs in Steps 3 through 5.

Unless the site investigation during Step 6 discovers unexpected information, the risk assessment should move smoothly through the risk characterization phase, because the data interpretation procedures were specified in the WP and SAP. While it might be informative to investigate a data set for trends, outliers, or other statistical indicators, these investigations should be secondary to the data interpretations specified in the SAP. Analysis of the data beyond the purposes for which it was collected might be informative, but could lead to biased, conflicting, or superfluous conclusions. Those outcomes can divert or confound the risk characterization process.

For ecological risk assessments that entail more than one type of study (or line of evidence), a strength-of-evidence approach is used to integrate different types of data to support a conclusion. The data might include toxicity test results, assessments of existing impacts at a site, or risk calculations comparing exposures estimated for the site with toxicity values from the literature. Balancing and interpreting the different types of data can be a major task and require professional judgment. As indicated above, the strength of evidence provided by different types of tests and the precedence that one type of study might have over another should already have been established during Step 4. Taking this approach will ensure that data interpretation is objective and not biased to support a preconceived answer. Additional strength-of-evidence considerations at this stage include the degree to which DQOs were met and whether confounding factors became evident during the site investigation and analysis phase.

For some biological tests (e.g., toxicity tests, benthic macroinvertebrate studies), all or some of the data interpretation process is outlined in existing documents, such as in toxicity testing manuals. However, in most cases, the SAP must provide the details on how the data are to be interpreted for a site. The data interpretation methods also should be presented in the risk characterization documentation. For example, if the triad approach was used to evaluate contaminated sediments, the risk estimation section should describe how the three types of studies (i.e., toxicity test, benthic invertebrate survey, and sediment chemistry) are integrated to draw conclusions about risk.

Where exposure-response functions are not available or developed, the quotient method of comparing an estimated exposure concentration to a threshold for response can be used, as in Step 2. Whenever possible, however, presentation of full exposure-response functions provides the risk manager with more information on which to base site decisions. This guidance has recommended the use of on-site contamination gradients to demonstrate on-site exposure-response functions. Where such data have been collected, they should be presented along with the risk estimates. Hazard quotients, hazard indices (for contaminants with the same mechanism of toxicity), the results of *in situ* toxicity testing, or community survey data can be mapped along with analytic chemistry data to provide a clear picture of the relationship between areas of contamination and effects.

In addition to developing point estimates of exposure concentrations, as for the hazard quotient approach, it might be possible to develop a distribution of exposure levels based on the potential variability in various exposure parameters (see Section 7.3.2). Probabilities of exceeding a threshold for adverse effects might then be estimated. Again, the risk assessment team and risk manager should have already agreed to what analyses will be used to characterize risks.

7.3 RISK DESCRIPTION

A key to risk description for Superfund sites is documentation of environmental contamination levels that bound the threshold for adverse effects on the assessment endpoints (Section 7.3.1). The risk description can also provide information to help the risk manager judge the likelihood and ecological significance of the estimated risks (Sections 7.3.2 and 7.3.3, respectively).

7.3.1 Threshold for Effects on Assessment Endpoints

Key outputs of the risk characterization step are contaminant concentrations in each environmental medium that bound the threshold for estimated adverse ecological effects given the uncertainty inherent in the data and models used. The lower bound of the threshold would be based on consistent conservative assumptions and NOAEL toxicity values. The upper bound would be based on observed impacts or predictions that ecological impacts could occur. This upper bound would be developed using consistent assumptions, site-specific data, LOAEL toxicity values, or an impact evaluation.

The approach to estimating environmental contaminant concentrations that represent thresholds for adverse ecological effects should have been specified in the study design (Step 4). When higher-trophic-level organisms are associated with assessment endpoints, the study design should have described how monitoring data and contaminant-transfer models would be used to back-calculate an environmental concentration representing a threshold for effect. If the site investigation demonstrated a gradient of ecological effects along a contamination gradient, the risk assessment team can identify and document the levels of contamination below which no further improvements in the assessment endpoints are discernable or expected. If departures from the original analysis plan are necessary based on information obtained during the site investigation or data analysis phase, the reasons for change should be documented.

When assessment endpoints include populations of animals that can travel moderate distances, different ways of presenting a threshold for adverse effects are possible. Various combinations of level of contamination and areal extent of contamination relative to the foraging range of the animals can result in similar contaminant intake levels by the animals. In that case, a point of departure for identifying a threshold for effect would be to identify that level of contamination, which if uniformly distributed both at the site and beyond, would

not pose a threat. The assumption of uniform contamination has been used to back-calculate water-quality criteria to protect piscivorous wildlife in the Great Lakes (U.S. EPA, 1995a). Again, use of this approach should have been specified in the study design.

7.3.2 Likelihood of Risk

In addition to identifying one or more thresholds for effects, the risk assessment team might develop estimates of the probability that exposure levels would exceed the ecotoxicity thresholds given the distribution of values likely for various exposure parameters (e.g., home range size, population density). A distributional analysis might be used to estimate the range of likely exposure levels associated with a given exposure model based on ranges for the input variables.

7.3.3 Additional Risk Information

In addition to developing numerical estimates of existing impacts, risks, and thresholds for effect, the risk assessor should put the estimates in context with a description of their extent, magnitude, and potential ecological significance. Additional ecological risk descriptors are listed below:

- The location and areal extent of existing contamination above a threshold for adverse effects;
- The degree to which the threshold for contamination is exceeded or is likely to be exceeded in the future, particularly if exposure-response functions are available; and
- The expected half-life (qualitative or quantitative) of contaminants in the environment (e.g., sediments, food chain) and the potential for natural recovery once the sources of contamination are removed.

To interpret the information in light of remedial options, the risk manager might need to solicit input from specific experts.

At this stage, it is important for the risk assessors to consider carefully several principles of risk communication, as described in U.S. EPA's (1996a) *Proposed Guidelines for Ecological Risk Assessment.*

7.4 UNCERTAINTY ANALYSIS

There are several sources of uncertainties associated with Superfund ecological risk estimates. One is the initial selection of substances of concern based on the sampling data and available toxicity information. Other sources of uncertainty include estimates of toxicity

to ecological receptors at the site based on limited data from the laboratory (usually on other species), from other ecosystems, or from the site over a limited period of time. Additional uncertainties result from the exposure assessment, as a consequence of the uncertainty in chemical monitoring data and models used to estimate exposure concentrations or doses. Finally, further uncertainties are included in risk estimates when simultaneous exposures to multiple substances occur.

Uncertainty should be distinguished from variability, which arises from true heterogeneity or variation in characteristics of the environment and receptors. Uncertainty, on the other hand, represents lack of knowledge about certain factors which can sometimes be reduced by additional study.

This section briefly notes several categories of uncertainty (Section 7.4.1) and techniques for tracking uncertainty through a risk assessment (Section 7.4.2). Additional guidance on discussing uncertainty and variability in risk characterization is provided in U.S. EPA's (1992f) *Guidance on Risk Characterization for Risk Managers and Risk Assessors.*

7.4.1 Categories of Uncertainty

There are three basic categories of uncertainties that apply to Superfund site risk assessments: (1) conceptual model uncertainties; (2) natural variation and parameter error; and (3) model error. Each of these is described below.

There will be uncertainties associated with the conceptual model used as the basis to investigate the site. The initial characterization of the ecological problems at a Superfund site, likely exposure pathways, chemicals of concern, and exposed ecological components, requires professional judgments and assumptions. To the extent possible, the risk assessment team should describe what judgments and assumptions were included in the conceptual model that formed the basis of the WP and SAP.

Parameter values (e.g., water concentrations, tissue residue levels, food ingestion rates) usually can be characterized as a distribution of values, described by central tendencies, ranges, and percentiles, among other descriptors. When evaluating uncertainty in parameter values, it is important to distinguish uncertainty from variability. Ecosystems include highly variable abiotic (e.g., weather, soils) and biotic (e.g., population density) components. If all instances of a parameter (e.g., all members of a population) could be sampled, the "true" parameter value distribution could be described. In practical terms, however, only a fraction of the instances (e.g., a few of the members of the population) can be sampled, leaving uncertainty concerning the true parameter value distribution. The risk assessor should provide either quantitative or qualitative descriptions of uncertainties in parameter value distributions.

Finally, there is uncertainty associated with how well a model (e.g., fate and transport model) approximates true relationships between site-specific environmental conditions. Models available at present tend to be fairly simple and at best, only partially validated with

field tests. As a consequence, it is important to identify key model assumptions and their potential impacts on the risk estimates.

7.4.2 Tracking Uncertainties

In general, there are two approaches to tracking uncertainties through a risk assessment: (1) using various point estimates of exposure and response to develop one or more point estimates of risk; and (2) conducting a distributional analysis to predict a distribution of risks based on a distribution of exposure levels and exposure-response information. Whether one or the other or both approaches are taken should have been agreed to during Step 4, and the specific type of analyses to be conducted should have been specified in the SAP.

7.5 SUMMARY

Risk characterization integrates the results of the exposure profile and exposure-response analyses, and is the final phase of the risk assessment process. It consists of risk estimation and risk description, which together provide information to help judge the ecological significance of risk estimates in the absence of remedial activities. The risk description also identifies a threshold for effects on the assessment endpoint as a range between contamination levels identified as posing no ecological risk and the lowest contamination levels identified as likely to produce adverse ecological effects. To ensure that the risk characterization is transparent, clear, and reasonable, information regarding the strengths and limitations of the assessment must be identified and described.

STEP 8: RISK MANAGEMENT

OVERVIEW

Risk management at a Superfund site is ultimately the responsibility of the site risk manager, who must balance risk reductions associated with cleanup of contaminants with potential impacts of the remedial actions themselves. The risk manager considers inputs from the risk assessors, BTAGs, stakeholders, and other involved parties. In Step 7, the risk assessment team identified a threshold for effects on the assessment endpoint as a range between contamination levels identified as posing no ecological risk and the lowest contamination levels identified as likely to produce adverse ecological effects. In Step 8, the risk manager evaluates several factors in deciding whether or not to clean up to within that range.

8.1 INTRODUCTION

Risk management is a distinctly different process from risk assessment (NRC, 1983, 1994; U.S. EPA, 1984a, 1995f). The risk assessment establishes whether a risk is present and defines a range or magnitude of the risk. In risk management, the results of the risk assessment are integrated with other considerations to make and justify risk management decisions. Additional risk management considerations can include the implications of existing background levels of contamination, available technologies, tradeoffs between human and ecological concerns, costs of alternative actions, and remedy selection. For further information on management of ecological risks Agency-wide, see U.S. EPA 1994h. Some Superfund-specific considerations are described below.

8.2 ECOLOGICAL RISK MANAGEMENT IN SUPERFUND

According to section 300.40 of the NCP, the purpose of the remedy selection process is to eliminate, reduce, or control risks to human health and the environment. The NCP indicates further that the results of the baseline risk assessment will help to establish acceptable exposure levels for use in developing remedial alternatives during the FS. Based on the criteria for selecting the preferred remedy and, using information from the human health and ecological risk assessments and the evaluation of remedial options in the FS, the risk manager then selects a preferred remedy.

The risk manager must consider several types of information in addition to the baseline ecological risk assessment when evaluating remedial options (Section 8.2.1). Of

particular concern for ecological risk management at Superfund sites is the potential for remedial actions themselves to cause adverse ecological impacts (Section 8.2.2). There also exists the opportunity to monitor ecological components at the site to gauge the effectiveness (or impacts) of the selected remedy (Section 8.2.3).

8.2.1 Other Risk Management Considerations

The baseline ecological risk assessment is not the only set of information that the risk manager must consider when evaluating remedial options during the FS phase of the Superfund process. The NCP (40 CFR 300.430(f)(1)(i)) specifies that each remedial alternative should be evaluated according to nine criteria. Two are considered threshold criteria, and take precedence over the others:

(1) Overall protection of human health and the environment; and

(2) Compliance with applicable or relevant and appropriate requirements (ARARs) (unless waiver applicable).

As described in Section 8.2.2 below, a particularly important consideration for the first criterion are the ecological impacts of the remedial options.

Five of the nine criteria are considered primary balancing criteria to be considered after the threshold criteria:

(3) Long-term effectiveness and permanence;

(4) Reduction of toxicity, mobility, or volume of hazardous wastes through the use of treatment;

(5) Short-term effectiveness;

(6) Implementability; and

(7) Cost.

Finally, two additional criteria are referred to as modifying criteria that must be considered:

(8) State acceptance, and

(9) Community acceptance.

Effective risk communication is particularly important to help ensure that a remedial option that best satisfies the other criteria can be implemented at a site. U.S. EPA's (1996a)

Proposed Guidelines for Ecological Risk Assessment provides an overview of this topic and identifies some of the relevant literature.

Additional factors that the site risk manager takes into consideration include existing background levels (see U.S. EPA, 1994g); current and likely future land uses (see U.S. EPA, 1995c); current and likely future resource uses in the area; and local, regional, and national ecological significance of the site. Consideration of the ecological impacts of remedial options and residual risks associated with leaving contaminants in place are very important considerations, as described in the next section.

8.2.2 Ecological Impacts of Remedial Options

Management of ecological risks must take into account the potential for impacts to the ecological assessment endpoints from implementation of various remedial options. The risk manager must balance: (1) residual risks posed by site contaminants before and after implementation of the selected remedy with (2) the potential impacts of the selected remedy on the environment independent of contaminant effects. The selection of a remedial alternative could require tradeoffs between long-term and short-term risk.

The ecological risks posed by the "no action" alternative are the risks estimated by the baseline ecological risk assessment. In addition, each remedial option is likely to have its own ecological impact. This impact could be anything from a short-term loss to complete and permanent loss of the present habitat and ecological communities. In instances where substantial ecological impacts will result from the remedy (e.g., dredging a wetland), the risk manager will need to consider ways to mitigate the impacts of the remedy and compare the mitigated impacts to the threats posed by the site contamination.

During the FS, the boundaries of potential risk under the no-action alternative (i.e., baseline conditions) can be compared with the evaluation of potential impacts of the remedial options to help justify the preferred remedy. As indicated above, the preferred remedy should minimize the risk of long-term impacts that could result from the remedy and any residual contamination. When the selected remedial option leaves some site contaminants presumed to pose an ecological risk in place, the justification for the selected remedy must be clearly documented.

In short, consideration of the environmental effects of the remedy itself might result in a decision to allow contaminants to remain on site at levels higher than the threshold for effects on the assessment endpoint. Thus, selection of the most appropriate ecologically based remedy can result in residual contamination that presents some risk.

8.2.3 Monitoring

Ecological risk assessment is a relatively new field with limited data available to validate its predictions. At sites where remedial actions are taken to reduce ecological

impacts and risks, the results of the remediation efforts should be compared with the predictions made during the ecological risk assessment.

While it often is difficult to demonstrate the effectiveness of remedial actions in reducing human health risks, it often is possible to demonstrate the effectiveness of remediations to reduce ecological risks, particularly if a several-year monitoring program is established. The site conceptual model provides the conceptual basis for monitoring options, and the site investigation should have indicated which options might be most practical for the site. Monitoring also is important to assess the effectiveness of a no-action alternative. For example, monitoring sediment contamination and benthic communities at intervals following removal of a contaminant source allows one to test predictions of the potential for the ecosystem to recover naturally over time.

8.3 SCIENTIFIC/MANAGEMENT DECISION POINT (SMDP)

The risk management decision is finalized in the Record of Decision (ROD). The decision should minimize the risk of long-term impacts that could result from the remedy and any residual contamination. When the selected remedy leaves residual contamination at levels higher than the upper-bound estimate of the threshold for adverse effects on the assessment endpoint, the risk manager should justify the decision (e.g., describe how a more complete physical remedy could jeopardize an ecological community more than the residual contamination).

8.4 SUMMARY

Risk-management decisions are the responsibility of the risk manager (the site manager), not the risk assessor. The risk manager should have been involved in planning the risk assessment; knowing the options available for reducing risks, the risk manager can help to frame questions during the problem-formulation phase of the risk assessment.

The risk manager must understand the risk assessment, including its uncertainties, assumptions, and level of resolution. With an understanding of potential adverse effects posed by residual levels of site contaminants and posed by the remedial actions themselves, the risk manager can balance the ecological costs and benefits of the available remedial options. Understanding the uncertainties associated with the risk assessment also is critical to evaluating the overall protectiveness of any remedy.

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This combined reference list and bibliography is intended to provide a broad, but not all inclusive, list of other materials that may provide useful information for ecological risk assessments at Superfund sites. These documents include other Superfund Program guidance documents, standard guides for toxicity testing, other EPA program office references with potential applications at Superfund sites, and other ecological risk assessment reference materials. References cited in the text are marked with an asterisk (*).

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GLOSSARY

This glossary includes definitions from several sources. A superscript number next to a word identifies the reference from which the definition was adapted (listed at the end of the Glossary).

Abiotic.[1] Characterized by absence of life; abiotic materials include non-living environmental media (e.g., water, soils, sediments); abiotic characteristics include such factors as light, temperature, pH, humidity, and other physical and chemical influences.

Absorption Efficiency. A measure of the proportion of a substance that a living organism absorbs across exchange boundaries (e.g., gastrointestinal tract).

Absorbed Dose.[2] The amount of a substance penetrating the exchange boundaries of an organism after contact. Absorbed dose for the inhalation and ingestion routes of exposure is calculated from the intake and the absorption efficiency. Absorbed dose for dermal contact depends on the surface area exposed and absorption efficiency.

Accuracy.[4] The degree to which a measurement reflects the true value of a variable.

Acute.[5] Having a sudden onset or lasting a short time. An acute stimulus is severe enough to induce a response rapidly. The word acute can be used to define either the exposure or the response to an exposure (effect). The duration of an acute aquatic toxicity test is generally 4 days or less and mortality is the response usually measured.

Acute Response. The response of (effect on) an organisms which has a rapid onset. A commonly measured rapid-onset response in toxicity tests is mortality.

Acute Tests. A toxicity test of short duration, typically 4 days or less (i.e., of short duration relative to the lifespan of the test organism).

Administered Dose.[2] The mass of a substance given to an organism and in contact with an exchange boundary (i.e., gastrointestinal tract) per unit wet body weight (BW) per unit time (e.g., mg/kgBW/day).

Adsorption.[14] Surface retention of molecules, atoms, or ions by a solid or liquid, as opposed to absorption, which is penetration of substances into the bulk of a solid or liquid.

Area Use Factor. The ratio of an organism's home range, breeding range, or feeding/foraging range to the area of contamination of the site under investigation.

Assessment Endpoint.[6] An explicit expression of the environmental value that is to be protected.

Benthic Community.[7] The community of organisms dwelling at the bottom of a pond, river, lake, or ocean.

Bioaccumulation.[5] General term describing a process by which chemicals are taken up by an organism either directly from exposure to a contaminated medium or by consumption of food containing the chemical.

Bioccumulation Factor (BAF).[3] The ratio of the concentration of a contaminant in an organism to the concentration in the ambient environment at steady state, where the organism can take in the contaminant through ingestion with its food as well as through direct contact.

Bioassay.[5] Test used to evaluate the relative potency of a chemical by comparing its effect on living organisms with the effect of a standard preparation on the same type of organism. Bioassay and toxicity tests are not the same—see toxicity test. Bioassays often are run on a series of dilutions of whole effluents.

Bioassessment. A general term referring to environmental evaluations involving living organisms; can include bioassays, community analyses, etc.

Bioavailability.[4] The degree to which a material in environmental media can be assimilated by an organism.

Bioconcentration.[5] A process by which there is a net accumulation of a chemical directly from an exposure medium into an organism.

Biodegrade.[15] Decompose into more elementary compounds by the action of living organisms, usually referring to microorganisms such as bacteria.

Biomagnification.[5] Result of the process of bioaccumulation and biotransfer by which tissue concentrations of chemicals in organisms at one trophic level exceed tissue concentrations in organisms at the next lower trophic level in a food chain.

Biomarker.[21] Biochemical, physiological, and histological changes in organisms that can be used to estimate either exposure to chemicals or the effects of exposure to chemicals.

Biomonitoring.[5] Use of living organisms as "sensors" in environmental quality surveillance to detect changes in environmental conditions that might threaten living organisms in the environment.

Body Burden. The concentration or total amount of a substance in a living organism; implies accumulation of a substance above background levels in exposed organisms.

Breeding Range. The area utilized by an organism during the reproductive phase of its life cycle and during the time that young are reared.

Bulk Sediment.[8] Field collected sediments used to conduct toxicity tests; can contain multiple contaminants and/or unknown concentrations of contaminants.

Characterization of Ecological Effects.[6] A portion of the analysis phase of ecological risk assessment that evaluates the ability of a stressor to cause adverse effects under a particular set of circumstances.

Characterization of Exposure.[6] A portion of the analysis phase of ecological risk assessment that evaluates the interaction of the stressor with one or more ecological components. Exposure can be expressed as co-occurrence, or contact depending on the stressor and ecological component involved.

Chemicals of Potential Concern.[2] Chemicals that are potentially site-related and whose data are of sufficient quality for use in a quantitative risk assessment.

Chronic.[5] Involving a stimulus that is lingering or continues for a long time; often signifies periods from several weeks to years, depending on the reproductive life cycle of the species. Can be used to define either the exposure or the response to an exposure (effect). Chronic exposures typically induce a biological response of relatively slow progress and long duration.

Chronic Response. The response of (or effect on) an organism to a chemical that is not immediately or directly lethal to the organism.

Chronic Tests.[9] A toxicity test used to study the effects of continuous, long-term exposure of a chemical or other potentially toxic material on an organism.

Community.[6] An assemblage of populations of different species within a specified location and time.

Complexation.[14] Formation of a group of compounds in which a part of the molecular bonding between compounds is of the coordinate type.

Concentration. The relative amount of a substance in an environmental medium, expressed by relative mass (e.g., mg/kg), volume (ml/L), or number of units (e.g., parts per million).

Concentration-Response Curve.[5] A curve describing the relationship between exposure concentration and percent of the test population responding.

Conceptual Model.[6] Describes a series of working hypotheses of how the stressor might affect ecological components. Describes ecosystem or ecosystem components potentially at

risk, and the relationships between measurement and assessment endpoints and exposure scenarios.

Contaminant of (Ecological) Concern. A substance detected at a hazardous waste site that has the potential to affect ecological receptors adversely due to its concentration, distribution, and mode of toxicity.

Control.[5] A treatment in a toxicity test that duplicates all the conditions of the exposure treatments but contains no test material. The control is used to determine the response rate expected in the test organisms in the absence of the test material.

Coordinate Bond.[14] A chemical bond between two atoms in which a shared pair of electrons forms the bond and the pair of electrons has been supplied by one of the two atoms. Also known as a coordinate valence.

Correlation.[10] An estimate of the degree to which two sets of variables vary together, with no distinction between dependent and independent variables.

Critical Exposure Pathway. An exposure pathway which either provides the highest exposure levels or is the primary pathway of exposure to an identified receptor of concern.

Degradation.[14] Conversion of an organic compound to one containing a smaller number of carbon atoms.

Deposition.[14] The lying, placing, or throwing down of any material.

Depuration.[5] A process that results in elimination of toxic substances from an organism.

Depuration Rate. The rate at which a substance is depurated from an organism.

Dietary Accumulation.[9] The net accumulation of a substance by an organism as a result of ingestion in the diet.

Direct Effect (toxin).[6] An effect where the stressor itself acts directly on the ecological component of interest, not through other components of the ecosystem.

Dose.[11] A measure of exposure. Examples include (1) the amount of a chemical ingested, (2) the amount of a chemical absorbed, and (3) the product of ambient exposure concentration and the duration of exposure.

Dose-Response Curve.[5] Similar to concentration-response curve except that the dose (i.e. the quantity) of the chemical administered to the organism is known. The curve is plotted as Dose versus Response.

Duplicate.[8] A sample taken from and representative of the same population as another sample. Both samples are carried through the steps of sampling, storage, and analysis in an identical manner.

Ecological Component.[6] Any part of an ecosystem, including individuals, populations, communities, and the ecosystem itself.

Ecological Risk Assessment.[6] The process that evaluates the likelihood that adverse ecological effects may occur or are occurring as a result of exposure to one or more stressors.

Ecosystem.[6] The biotic community and abiotic environment within a specified location and time, including the chemical, physical, and biological relationships among the biotic and abiotic components.

Ecotoxicity.[11] The study of toxic effects on nonhuman organisms, populations, or communities.

Estimated or Expected Environmental Concentration.[5] The concentration of a material estimated as being likely to occur in environmental media to which organisms are exposed.

Exposure.[6] Co-occurrence of or contact between a stressor and an ecological component. The contact reaction between a chemical and a biological system, or organism.

Exposure Assessment.[2] The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure.

Exposure Pathway.[2] The course a chemical or physical agent takes from a source to an exposed organism. Each exposure pathway incudes a source or release from a source, an exposure point, and an exposure route. If the exposure point differs from the source, transport/exposure media (i.e., air, water) also are included.

Exposure Pathway Model. A model in which potential pathways of exposure are identified for the selected receptor species.

Exposure Point.[2] A location of potential contact between an organism and a chemical or physical agent.

Exposure Point Concentration. The concentration of a contaminant occurring at an exposure point.

Exposure Profile.[6] The product of characterizing exposure in the analysis phase of ecological risk assessment. The exposure profile summarizes the magnitude and spatial and temporal patterns of exposure for the scenarios described in the conceptual model.

Exposure Route.[2] The way a chemical or physical agent comes in contact with an organism (i.e., by ingestion, inhalation, or dermal contact).

Exposure Scenario.[6] A set of assumptions concerning how an exposure takes place, including assumptions about the exposure setting, stressor characteristics, and activities of an organism that can lead to exposure.

False Negative. The conclusion that an event (e.g., response to a chemical) is negative when it is in fact positive (see Appendix D).

False Positive. The conclusion that an event is positive when it is in fact negative (see Appendix D).

Fate.[5] Disposition of a material in various environmental compartments (e.g. soil or sediment, water, air, biota) as a result of transport, transformation, and degradation.

Food-Chain Transfer. A process by which substances in the tissues of lower-trophic-level organisms are transferred to the higher-trophic-level organisms that feed on them.

Forage (feeding) Area. The area utilized by an organism for hunting or gathering food.

Habitat.[1] Place where a plant or animal lives, often characterized by a dominant plant form and physical characteristics.

Hazard. The likelihood that a substance will cause an injury or adverse effect under specified conditions.

Hazard Identification.[2] The process of determining whether exposure to a stressor can cause an increase in the incidence of a particular adverse effect, and whether an adverse effect is likely to occur.

Hazard Index.[3] The sum of more than one hazard quotient for multiple substances and/or multiple exposure pathways. The HI is calculated separately for chronic, subchronic, and shorter-duration exposures.

Hazard Quotient.[2] The ratio of an exposure level to a substance to a toxicity value selected for the risk assessment for that substance (e.g., LOAEL or NOAEL).

Home Range.[12] The area to which an animal confines its activities.

Hydrophilic.[22] Denoting the property of attracting or associating with water molecules; characteristic of polar or charged molecules.

Hydrophobic.[12] With regard to a molecule or side group, tending to dissolve readily in organic solvents, but not in water, resisting wetting, not containing polar groups or sub-groups.

Hypothesis.[12] A proposition set forth as an explanation for a specified phenomenon or group of phenomena.

Indirect Effect.[6] An effect where the stressor acts on supporting components of the ecosystem, which in turn have an effect on the ecological component of interest.

Ingestion Rate. The rate at which an organism consumes food, water, or other materials (e.g., soil, sediment). Ingestion rate usually is expressed in terms of unit of mass or volume per unit of time (e.g., kg/day, L/day).

Ionization.[14] The process by which a neutral atom loses or gains electrons, thereby acquiring a net charge and becoming an ion.

Lethal.[5] Causing death by direct action.

Lipid.[13] One of a variety of organic substances that are insoluble in polar solvents, such as water, but that dissolve readily in non-polar organic solvents. Includes fats, oils, waxes, steroids, phospholipids, and carotenes.

Lowest-Observable-Adverse-Effect Level (LOAEL). The lowest level of a stressor evaluated in a toxicity test or biological field survey that has a statistically significant adverse effect on the exposed organisms compared with unexposed organisms in a control or reference site.

Matrix.[14] The substance in which an analyte is embedded or contained; the properties of a matrix depend on its constituents and form.

Measurement Endpoint.[6] A measurable ecological characteristic that is related to the valued characteristic chosen as the assessment endpoint. Measurement endpoints often are expressed as the statistical or arithmetic summaries of the observations that make up the measurement. As used in this guidance document, measurement endpoints can include measures of effect and measures of exposure, which is a departure from U.S. EPA's (1992a) definition which includes only measures of effect.

Media.[15] Specific environmental compartments—air, water, soil—which are the subject of regulatory concern and activities.

Median Effective Concentration (EC_{50}).[5] The concentration of a substance to which test organisms are exposed that is estimated to be effective in producing some sublethal response in 50 percent of the test population. The EC_{50} usually is expressed as a time-dependent value

(e.g., 24-hour EC_{50}). The sublethal response elicited from the test organisms as a result of exposure must be clearly defined.

Median Lethal Concentration (LC_{50}).[5] A statistically or graphically estimated concentration that is expected to be lethal to 50 percent of a group of organisms under specified conditions.

Metric.[16] Relating to measurement; a type of measurement—for example a measurement of one of various components of community structure (e.g., species richness, % similarity).

Mortality. Death rate or proportion of deaths in a population.

No-Observed-Adverse-Effect Level (NOAEL).[5] The highest level of a stressor evaluated in a toxicity test or biological field survey that causes no statistically significant difference in effect compared with the controls or a reference site.

Nonparametric.[17] Statistical methods that make no assumptions regarding the distribution of the data.

Parameter.[18] Constants applied to a model that are obtained by theoretical calculation or measurements taken at another time and/or place, and are assumed to be appropriate for the place and time being studied.

Parametric.[14] Statistical methods used when the distribution of the data is known.

Population.[6] An aggregate of individuals of a species within a specified location in space and time.

Power.[10] The power of a statistical test indicates the probability of rejecting the null hypothesis when it should be rejected (i.e., the null hypothesis is false). Can be considered the sensitivity of a statistical test. (See also Appendix D.)

Precipitation.[14] In analytic chemistry, the process of producing a separable solid phase within a liquid medium.

Precision.[19] A measure of the closeness of agreement among individual measurements.

Reference Site.[11] A relatively uncontaminated site used for comparison to contaminated sites in environmental monitoring studies, often incorrectly referred to as a control.

Regression Analysis.[10] Analysis of the functional relationship between two variables; the independent variable is described on the X axis and the dependent variable is described on the Y axis (i.e, the change in Y is a function of a change in X).

Replicate. Duplicate analysis of an individual sample. Replicate analyses are used for quality control.

Representative Samples.[18] Serving as a typical or characteristic sample; should provide analytical results that correspond with actual environmental quality or the condition experienced by the contaminant receptor.

Risk.[5] The expected frequency or probability of undesirable effects resulting from exposure to known or expected stressors.

Risk Characterization.[6] A phase of ecological risk assessment that integrates the results of the exposure and ecological effects analyses to evaluate the likelihood of adverse ecological effects associated with exposure to the stressor. The ecological significance of the adverse effects is discussed, including consideration of the types and magnitudes of the effects, their spatial and temporal patterns, and the likelihood of recovery.

Sample.[14] Fraction of a material tested or analyzed; a selection or collection from a larger collection.

Scientific/Management Decision Point (SMDP). A point during the risk assessment process when the risk assessor communicates results of the assessment at that stage to a risk manager. At this point the risk manager determines whether the information is sufficient to arrive at a decision regarding risk management strategies and/or the need for additional information to characterize risk.

Sediment.[20] Particulate material lying below water.

Sensitivity. In relation to toxic substances, organisms that are more sensitive exhibit adverse (toxic) effects at lower exposure levels than organisms that are less sensitive.

Sensitive Life Stage. The life stage (i.e., juvenile, adult, etc.) that exhibits the highest degree of sensitivity (i.e., effects are evident at a lower exposure concentration) to a contaminant in toxicity tests.

Species.[13] A group of organisms that actually or potentially interbreed and are reproductively isolated from all other such groups; a taxonomic grouping of morphologically similar individuals; the category below genus.

Statistic.[10] A computed or estimated statistical quantity such as the mean, the standard deviation, or the correlation coefficient.

Stressor.[6] Any physical, chemical, or biological entity that can induce an adverse response.

Sublethal.[5] Below the concentration that directly causes death. Exposure to sublethal concentrations of a substance can produce less obvious effects on behavior, biochemical and/or physiological functions, and the structure of cells and tissues in organisms.

Threshold Concentration.[5] A concentration above which some effect (or response) will be produced and below which it will not.

Toxic Mechanism of Action.[23] The mechanism by which chemicals produce their toxic effects, i.e., the mechanism by which a chemical alters normal cellular biochemistry and physiology. Mechanisms can include; interference with normal receptor-ligand interactions, interference with membranae functions, interference with cellular energy production, and binding to biomolecules.

Toxicity Assessment. Review of literature, results in toxicity tests, and data from field surveys regarding the toxicity of any given material to an appropriate receptor.

Toxicity Test.[5] The means by which the toxicity of a chemical or other test material is determined. A toxicity test is used to measure the degree of response produced by exposure to a specific level of stimulus (or concentration of chemical) compared with an unexposed control.

Toxicity Value.[2] A numerical expression of a substance's exposure-response relationship that is used in risk assessments.

Toxicant. A poisonous substance.

Trophic Level.[6] A functional classification of taxa within a community that is based on feeding relationships (e.g., aquatic and terrestrial plants make up the first trophic level, and herbivores make up the second).

Type I Error.[10] Rejection of a true null hypothesis (see also Appendix D).

Type II Error.[10] Acceptance of a false null hypothesis (see also Appendix D).

Uptake.[5] A process by which materials are transferred into or onto an organism.

Uncertainty.[11] Imperfect knowledge concerning the present or future state of the system under consideration; a component of risk resulting from imperfect knowledge of the degree of hazard or of its spatial and temporal distribution.

Volatilization.[14] The conversion of a chemical substance from a liquid or solid state to a gaseous vapor state.

Xenobiotic.[6] A chemical or other stressor that does not occur naturally in the environment. Xenobiotics occur as a result of anthropogenic activities such as the application of pesticides and the discharge of industrial chemicals to air, land, or water.

ENDNOTES

[1] Krebs 1978, [2] U.S. EPA 1989, [3] Calow 1993, [4] Freedman 1989, [5] Rand and Petrocelli 1985, [6] U.S. EPA 1992a, [7] Ricklefs 1990, [8] U.S. EPA 1992b, [9] ASTM 1993a, [10] Sokal and Rohlf 1981, [11] Suter 1993, [12] Wallace et al. 1981, [13] Curtis 1983, [14] Parker 1994, [15] Sullivan 1993, [16] U.S. EPA 1990, [17] Zar 1984, [18] Keith 1988, [19] Gilbert 1987, [20] ASTM 1993b, [21] Huggett et al. 1992, [22] Stedman 1995, [23] Amdur et al. 1991.

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APPENDIX A

EXAMPLE ECOLOGICAL RISK ASSESSMENTS FOR HYPOTHETICAL SITES

INTRODUCTION

Appendix A provides examples of Steps 1 through 5 of the ecological risk assessment process for three hypothetical sites:

(1) A former municipal landfill from which copper is leaching into a large pond down-gradient of the site (the copper site);

(2) A former chemical production facility that spilled DDT, which has been transported into a nearby stream by surface water runoff (the DDT site); and

(3) A former waste-oil recycling facility that disposed of PCBs in a lagoon from which extensive soil contamination has resulted (the PCB site).

These examples are intended to illustrate key points in Steps 1 through 5 of the ecological risk assessment process. No actual site is the basis for the examples.

The examples stop with Step 5 because the remaining steps (6 through 8) of the ecological risk assessment process and the risk management decisions depend on site-specific data collected during a site investigation. We have not attempted to develop hypothetical data for analysis or the full range of information that a site risk manager would consider when evaluating remedial options.

EXAMPLE 1: COPPER SITE

STEP 1: SCREENING-LEVEL PROBLEM FORMULATION AND ECOLOGICAL EFFECTS EVALUATION

Site history. This is a former municipal landfill located in an upland area of the mid-Atlantic plain. Residential, commercial, and industrial refuse was disposed of at this site in the 1960s and 1970s. Large amounts of copper wire also were disposed at this site over several years. Currently, minimal cover has been placed over the fill and planted with grasses. Terrestrial ecosystems in the vicinity of the landfill include upland forest and successional fields. Nearby land uses include agriculture and residential and commercial uses. The landfill cover has deteriorated in several locations. Leachate seeps have been noted on the slope of the landfill, and several seeps discharge to a five-acre pond down-gradient of the site.

Site visit. A preliminary site visit was conducted and the ecological checklist was completed. The checklist indicated that the pond has an organic substrate; emergent vegetation, including cattail and rushes, occurs along the shore near the leachate seeps; and the pond reaches a depth of five feet toward the middle. Fathead minnows, carp, and several species of sunfish were observed, and the benthic macroinvertebrate community appeared to be diverse. The pond water was clear, indicating an absence of phytoplankton. The pond appears to function as a valuable habitat for fish and other wildlife using this area. Preliminary sampling indicated elevated copper levels in the seep as well as elevated base cations, total organic carbon (TOC), and depressed pH levels (pH 5.7).

Problem formulation. Copper is leaching from the landfill into the pond from a seep area. EPA's ambient water quality criteria document for copper (U.S. EPA, 1985) indicates that it can cause toxic effects in aquatic plants, aquatic invertebrates, and young fish at relatively low water concentrations. Thus, the seep might threaten the ability of the pond to support macroinvertebrate and fish communities and the wildlife that feed on them. Terrestrial ecosystems do not need to be evaluated because the overland flow of the seeps is limited to short gullies, a few inches wide. Thus, the area of concern has been identified as the five-acre pond and the associated leachate seeps. Copper in surface water and sediments of the pond might be of ecological concern.

Ecological effects evaluation. Copper is toxic to both aquatic plants and aquatic animals. Therefore, aquatic toxicity-based data will be used to screen for ecological risk in the preliminary risk calculation. The screening ecotoxicity value selected for water-column exposure is the U.S. EPA chronic ambient water quality criterion (12 µg/L at a water hardness of 100 mg/L as $CaCO_3$). A screening ecotoxicity value for copper in sediments was identified as 34 mg/kg (U.S. EPA, 1996).

STEP 2: SCREENING-LEVEL EXPOSURE ESTIMATE AND RISK CALCULATION

Exposure estimate. Preliminary sampling data indicate that the leachate contains 53 µg/L copper as well as elevated base cations, elevated TOC, and depressed pH (pH 5.7). Sediment concentrations range from 300 mg/kg to below detection (2 mg/kg), decreasing with distance from the leachate seeps.

Risk calculation. The copper concentration in the seep water (53 µg/L) exceeds the chronic water quality criterion for copper (12 µg/L). The maximum sediment copper concentration of 300 mg/kg exceeds the screening ecotoxicity value for copper in sediments (34 mg/kg). Therefore, the screening-level hazard quotients for both sediment and water exceed one. The decision at the Scientific/Management Decision Point (SMDP) is to continue the ecological risk assessment.

Similar screening for the levels of base cations generated hazard quotients below one in the seep water. Although TOC and pH are not regulated under CERCLA, the possibility that those parameters might affect the biota of the pond should be kept in mind if surveys of the pond biota are conducted. Sediment concentrations of chemicals other than copper generated hazard quotients (HQs) of less than one at the maximum concentrations found.

STEP 3: BASELINE RISK ASSESSMENT PROBLEM FORMULATION

Based on the screening-level risk assessment, copper is known to be the only contaminant of ecological concern at the site.

Ecotoxicity literature review. A review of the literature on the ecotoxicity of copper to aquatic biota was conducted and revealed several types of information. Young aquatic organisms are more sensitive to copper than adults (Demayo et al., 1982; Kaplan and Yoh, 1961; Hubschman, 1965). Fish larvae usually are more sensitive than embryos (McKim et al., 1978; Weis and Weis, 1991), and fish become less sensitive to copper as body weight increases (Demayo et al., 1982). Although the exact mechanism of toxicity to fish is unknown, a loss of osmotic control has been noted in some studies (Demayo et al. 1982; Cheng and Sullivan, 1977).

Flowthrough toxicity studies in which copper concentrations were measured revealed LC_{50} values ranging from 75 to 790 µg/L for fathead minnows and 63 to 800 µg/L for common carp (U.S. EPA, 1985). Coldwater fish species, such as rainbow trout, can be more sensitive, and species like pumpkinseeds (a sunfish) and bluegills are less sensitive (U.S. EPA, 1985). Although fish fry usually are the most sensitive life stage, this is not always the case; Pickering et al. (1977) determined an LC_{50} of 460 µg/L to 6-month-old juveniles and an LC_{50} of 490 µg/L to 6-week-old fry for fathead minnows. A copper concentration in water of 37 µg/l has been shown to cause a significant reduction in fish egg production (Pickering et al., 1977).

Elevated levels of copper in sediments have been associated with changes in benthic community structure, notably reduced numbers of species (Winner et al., 1975; Kraft and Sypniewski, 1981). Studies also have been conducted with adult *Hyalella azteca* (an amphipod) exposed to copper in sediments. One of these studies indicated an LC_{50} of 1,078 mg/kg in the sediment (Cairns et al., 1984); however, a no-observed-adverse-effect level (NOAEL) for copper in sediments was not identified for an early life stage of a benthic invertebrate.

A literature review of the ecotoxicity of copper to aquatic plants, both algae and vascular plants, did not reveal information on the toxic mechanism by which copper affects plants. The review did indicate that exposure of plants to high copper levels inhibits photosynthesis and growth (U.S. EPA, 1985), and cell separation after cell division (Hatch, 1978). Several studies conducted using *Selenastrum capricornutum* indicated that concentrations at 300 µg/L kill algae after 7 days, and a value of 90 µg/l causes complete growth inhibition after 7 days (Bartlett et al., 1974).

The literature indicates that copper does not biomagnify in food chains and does not bioaccumulate in most animals because it is a biologically regulated essential element. Accumulation in phytoplankton and filter-feeding mollusks, however, does occur. The toxicity of copper in water is influenced by water hardness, alkalinity, and pH (U.S. EPA, 1985).

Exposure pathways. A flow diagram was developed to depict the environmental pathways that could result in impacts of copper to the pond's biota (see Exhibit A-1). Direct exposure to copper in the pond water and sediments could cause acute or chronic toxicity in early life stages of fish and/or benthic invertebrates, and in aquatic plants. Risks to filter-feeding mollusks and phytoplankton as well as animals that feed on them are not considered because the mollusks and phytoplankton are unlikely to occur in significant quantities in the pond. The exposure pathways that will be evaluated, therefore, are direct contact with contaminated sediments and water.

Assessment endpoints and conceptual model. Based on the screening-level risk assessment, the ecotoxicity literature review, and the complete exposure pathways, development of a conceptual model for the site is initiated. Copper can be acutely or chronically toxic to organisms in an aquatic community through direct exposure of the organisms to copper in the water and sediments. Threats of copper to higher trophic level organisms are unlikely to exceed threats to organisms at the base of the food chain, because copper is an essential nutrient which is effectively regulated by most organisms if the exposure is below toxic levels. Fish fry in particular can be very sensitive to copper in water.

Based on these receptors and the potential for both acute and chronic toxicity, an appropriate general assessment endpoint for the ecosystem would be the maintenance of the community composition of the pond. A more operational definition of the assessment endpoint would be the maintenance of pond community structure typical for the locality and

for the physical attributes of the pond, with no loss of species or community alteration due to copper toxicity.

Risk questions. One question is whether the concentrations of copper present in the sediments and water over at least part of the pond are toxic to aquatic plants or animals. A further question is what concentration of copper in sediments represents a threshold for adverse effects. That level could be used as a preliminary cleanup goal.

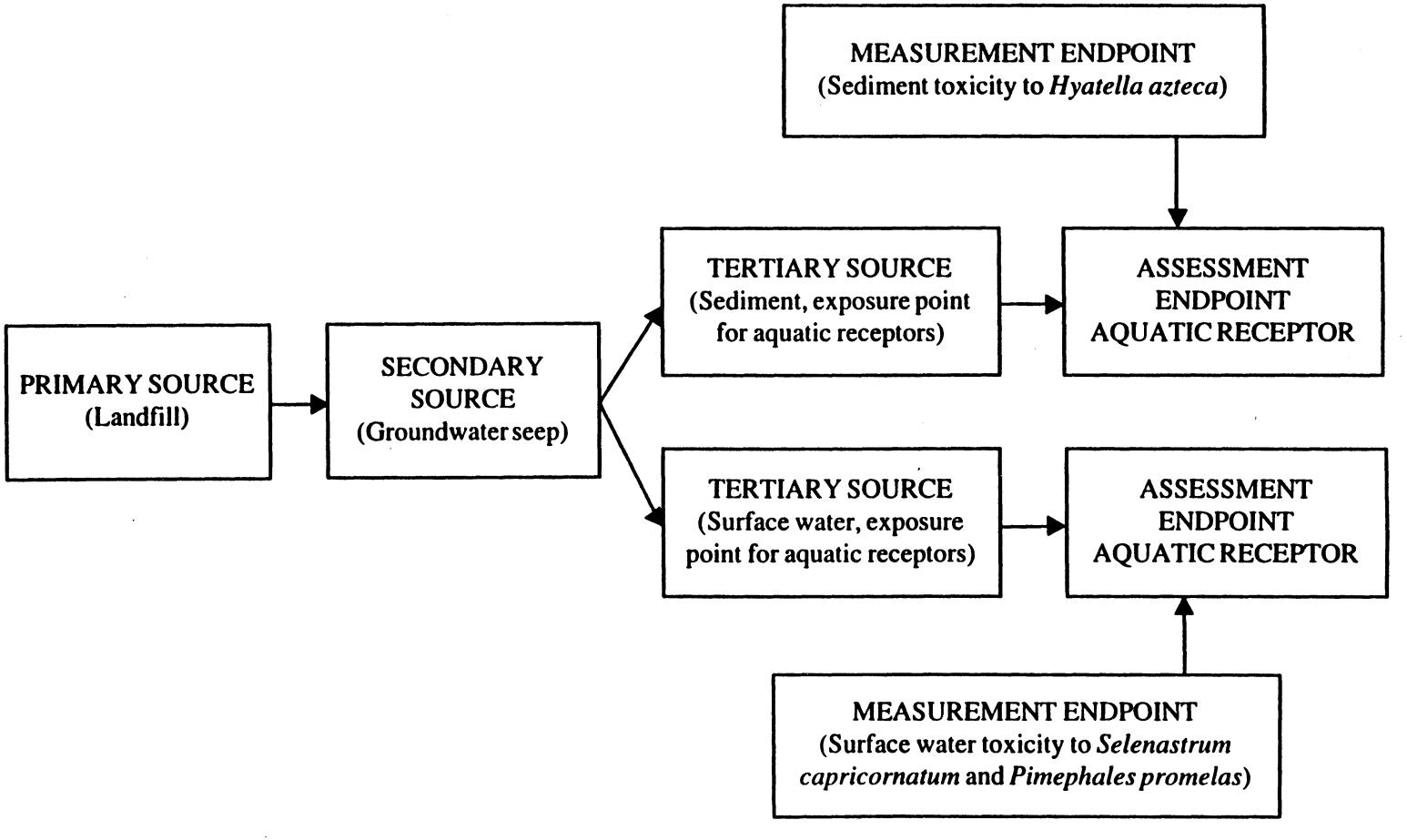
STEP 4: MEASUREMENT ENDPOINTS AND STUDY DESIGN

To answer the hypothesis identified in Step 3, three lines of evidence were considered when selecting measurement endpoints: (1) whether the ambient copper levels are higher than levels known to be directly toxic to aquatic organisms likely or known to be present in the pond; (2) whether water and sediments taken from the pond are more toxic to aquatic organisms than water and sediments from a reference pond; and (3) whether the aquatic community structure in the site pond is simplified relative to a reference pond.

Measurement endpoints. Since the identified assessment endpoint is maintaining a typical pond community structure, the possibility of directly measuring the condition of the plant, fish, and macroinvertebrate communities in the pond was considered. Consultation with experts on benthic macroinvertebrates suggested that standard measures of the pond benthic invertebrate community probably would be insensitive measures of existing effects at this particular site because of the high spatial variation in benthic communities within and among ponds of this size. Measuring the fish community also would be unsuitable, due to the limited size of the pond and low diversity of fish species anticipated. Since copper is not expected to bioaccumulate or biomagnify in this pond, direct toxicity testing was selected as appropriate. Because early life stages tend to be more sensitive to the toxic effects of copper than older life stages, chronic toxicity would be measured on early life stages. For animals, toxicity is defined as a statistically significant decrease in survival or juvenile growth rates (measurement endpoints) of a test group exposed to water or sediments from the site compared with a test group exposed to water or sediments from a reference site. For plants, toxicity is defined as a statistically significant decrease in growth rate (measurement endpoint) with the same comparison.

One toxicity test selected is a 10-day (i.e., chronic) solid-phase sediment toxicity test using an early life stage of *Hyalella azteca*. The measures of effects for the test are mortality rates and growth rates (measured as length and weight increases). Two water-column toxicity tests will be used: (1) a 7-day test using the alga *Selenastrum capricornutum* (growth test) and (2) a 7-day larval fish test using *Pimephales promelas* (mortality and growth endpoints). The *H. azteca* and *P. promelas* toxicity tests will be used to determine the effects of copper on early life stages of invertebrates and fish in sediment and the water column, respectively. The test on *S. capricornutum* will be used to determine the phytotoxicity of copper in the water column.

EXHIBIT A-1
Conceptual Model for the Copper Site



Study design. To answer the questions stated in the problem formulation step, the study design specified in the following. The water column tests will be run on 100 percent seep water, 100 percent pond water near the seep, 100 percent reference-site water, and the laboratory control. U.S. EPA test protocols will be followed. Five sediment samples will be collected from the pond bottom at intervals along the observed concentration gradient, from a copper concentration of 300 mg/kg at the leachate seeps down to approximately 5 mg/kg near the other end of the pond. The sediment sampling locations will transect the pond at equidistant locations and include the point of maximum pond depth. All sediment samples will be split so that copper concentrations can be measured in sediments from each sampling location. A reference sediment will be collected and a laboratory control will be run. Test organisms will not be fed during the test; sediments will be sieved to remove native organisms and debris. Laboratory procedures will follow established protocols and will be documented and reviewed prior to initiation of the test. For the water-column test, statistical comparisons will be made between responses to each of the two pond samples and the reference site, as well as the laboratory control. Statistical comparisons also will be made of responses to sediments taken from each sampling location and responses to the reference sediment sample.

Because leachate seeps can be intermittent (depending on rainfall), the study design specifies that a pre-sampling visit is required to confirm that the seep is flowing and can be sampled. The study design also specifies that both sediments and water will be sampled at the same time at each sampling location.

As the work plan (WP) and sampling and analysis plan (SAP) were finished, the ecological risk assessor and the risk manager agreed on the site conceptual model, assessment endpoints, and study design (SMDP).

STEP 5: FIELD VERIFICATION OF STUDY DESIGN

A site assessment was conducted two days prior to the scheduled initiation of the site investigation to confirm that the seep was active. It was determined that the seep was active and that the site investigation could be initiated.

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EXAMPLE 2: DDT SITE

STEP 1: SCREENING-LEVEL PROBLEM FORMULATION AND ECOLOGICAL EFFECTS EVALUATION

Site history. This is the site of a former chemical production facility located adjacent to a stream. The facility manufactured and packaged dichlorodiphenyltrichloroethane (DDT). Due to poor storage practices, several DDT spills have occurred.

Site visit. A preliminary site visit was conducted and the ecological checklist was completed. Information gathered indicates that surface water drainage from the site flows through several drainage swales toward an unnamed creek. This creek is a second-order stream containing riffle-run areas and small pools. The stream substrate is composed of sand and gravel in the pools with some depositional areas in the backwaters and primarily cobble in the riffles.

Problem formulation. Previous sampling efforts indicated the presence of DDT and its metabolites in the stream's sediments over several miles at concentrations up to 230 mg/kg. A variety of wildlife, especially piscivorous birds, use this area for feeding. Many species of minnow have been noted in this stream. DDT is well known for its tendency to bioaccumulate and biomagnify in food chains, and available evidence indicates that it can cause reproductive failure in birds due to eggshell thinning.

The risk assessment team and risk manager agreed that the assessment endpoint is adverse effects on reproduction of high-trophic-level wildlife, particularly piscivorous birds.

Ecological effects evaluation. Because DDT is well studied, a dietary concentration above which eggshell thinning might occur was identified in existing U.S. EPA documents on the ecotoxicity of DDT. Moreover, a no-observed-adverse-effect-level (NOAEL) for the ingestion route for birds also was identified.

STEP 2: SCREENING-LEVEL EXPOSURE ESTIMATE AND RISK CALCULATION

Exposure estimate. For the screening-level exposure estimate, maximum concentrations of DDT identified in the sediments were used. To estimate the concentration of DDT in forage fish, the maximum concentration in sediments was multiplied by the highest DDT bioaccumulation factor relating forage fish tissue concentrations to sediment concentrations reported in the literature. Moreover, it was assumed that the piscivorous birds obtain 100 percent of their diet from the contaminated area.

Risk calculation. The predicted concentrations of DDT in forage fish were compared with the dietary NOAEL for DDT in birds. This risk screen indicated that DDT concentrations measured at this site might be high enough to cause adverse reproductive

effects in birds. Thus, transfer of DDT from the sediments to the stream and biota are of concern at this site.

STEP 3: BASELINE RISK ASSESSMENT PROBLEM FORMULATION

Based on the screening-level risk assessment, potential bioaccumulation of DDT in aquatic food chains and effects of DDT on reproduction in piscivorous birds are known concerns. During refinement of the problem, the potential for additional ecological effects of DDT was examined.

Ecotoxicity literature review. In freshwater systems, DDT can have direct effects on animals, particularly aquatic insects. A literature review of the aquatic toxicity of DDT was conducted, and a NOAEL and LOAEL identified for the toxicity of DDT to aquatic insects. Aquatic plants are not affected by DDT. Additional quantitative information on effects of DDT on birds was reviewed, particularly to identify what level of eggshell thinning is likely to reduce reproductive success. A number of studies have correlated DDT residues measured in eggs of birds to increased eggshell thinning and egg loss due to breakage. Eggshell thinning of more than 20 percent appears to result in decreased hatching success due to eggshell breakage (Anderson and Hickey, 1972; Dilworth et al., 1972). Information was not available for any piscivorous species of bird. Lincer (1975) conducted a laboratory feeding study using American kestrels. Females fed a diet of 6 mg/kg DDE[1] (1.1 mg/kgBW-day) produced eggs with shells which were 25.5 percent thinner than archived eggshells collected prior to widespread use of DDT. Based on this information, a LOAEL of 1.1 mg/kgBW-day was selected to evaluate the effects of DDT on piscivorous birds.

Exposure pathways, assessment endpoints, and conceptual model. Based on knowledge of the fate and transport of DDT in aquatic systems and the ecotoxicity of DDT to aquatic organisms and birds, a conceptual model was initiated. DDT buried in the sediments can be released to the water column during resuspension and redistribution of the sediments. Some diffusion of DDT to the water column from the sediment surface also will occur. The benthic community would be an initial receptor for the DDT in sediments, which could result in reduced benthic species abundance and DDT accumulation in species that remain. Fish that feed on benthic organisms might be exposed to DDT both in the water column and in their food. Piscivorous birds would be exposed to the DDT that has accumulated in the fish, and could be exposed at levels sufficiently high to cause more than 20 percent eggshell thinning. Based on this information, two assessment endpoints were identified: (1) maintaining stream community structure typical for the stream order and location, and (2) protecting piscivorous birds from eggshell thinning that could result in reduced reproductive success.

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[1] DDE is a degradation product of DDT; typically, field measures of DDT are reported as the sum of the concentrations of DDT, DDE, and DDD (another degradation product).

A flow diagram of the exposure pathways for DDT was added to the conceptual model (Exhibit A-2). The diagram identifies the primary, secondary, and tertiary sources of DDT at the site, as well as the primary, secondary, and tertiary types of receptors that could be exposed.

Risk questions. Two questions were developed: (1) has the stream community been affected by the DDT, and (2) have food-chain accumulation and transfer of DDT occurred to the extent that 20 percent or more eggshell thinning would be expected in piscivorous birds that use the area.

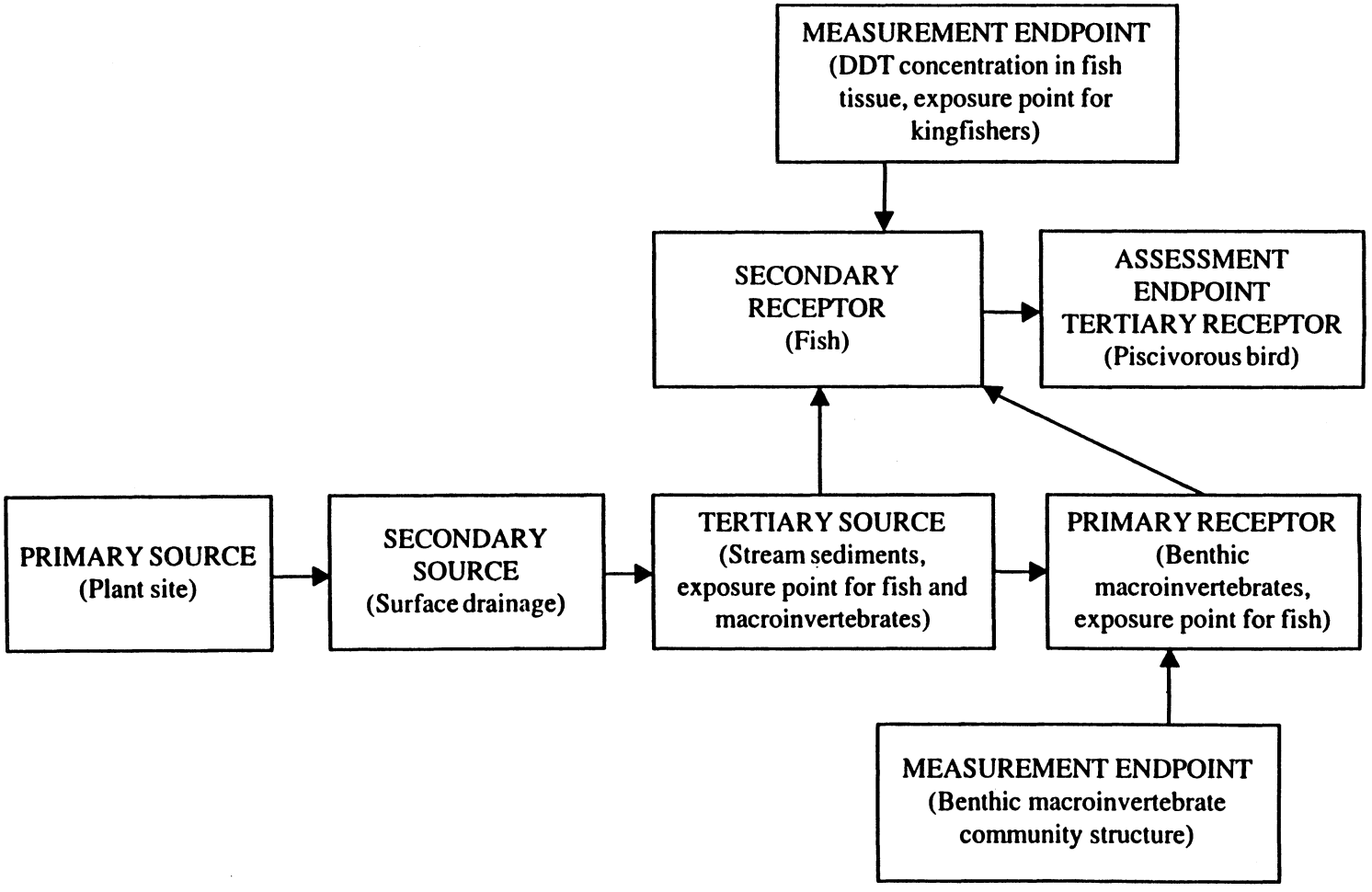
STEP 4: MEASUREMENT ENDPOINTS AND STUDY DESIGN

Measurement endpoints. For the assessment endpoint of protecting piscivorous birds from eggshell thinning, the conceptual model indicated that DDT in sediments could reach piscivorous birds through forage fish. Belted kingfishers are known to feed in the stream. They also have the smallest home range of the piscivorous birds in the area, which means that more kingfishers can forage entirely from the contaminated stream area than can other species of piscivorous birds. Thus, one can conclude that, if the risk assessment shows no threat of eggshell thinning to the kingfisher, there should be minimal or no threat to other piscivorous birds that might utilize the site. Eggshell thinning in the belted kingfisher therefore was selected as the measure of effect.

Data from the literature suggest that DDT can have a bioaccumulation factor in surface water systems as high as six orders of magnitude (10^6); however, in most aquatic ecosystems, the actual bioaccumulation of DDT from the environment is lower, often substantially lower. Many factors influence the actual accumulation of DDT in the environment. There is considerable debate over the parameters of any proposed theoretical bioaccumulation model; therefore, it was decided to measure tissue residue levels in the forage fish at the site instead of estimating the tissue residue levels in forage fish using a bioaccumulation factor (BAF).

Existing information on the distribution of DDT in the stream indicates that a general gradient of DDT concentrations exists in the sediments, and five locations could be identified that corresponded to a range of DDT concentrations in sediments. Based on information available on fish communities in streams similar to the one in the site area, creek chub (*Semotilus atromaculatus*) were selected to measure exposure levels for kingfishers. Creek chub feed on benthic invertebrates, which are in direct contact with the contaminated sediments. Adult creek chub average 10 inches and about 20 grams, allowing for analysis of individual fish. Creek chub also have small home ranges during the spring and summer, and thus it should be possible to relate DDT levels in the chub to DDT levels in the sediments.

EXHIBIT A-2
Conceptual Model for the Stream DDT Site



For the assessment endpoint of maintaining stream community structure, the selected measurement endpoints were several metrics describing the abundance and trophic structure of the stream benthic macroinvertebrate community.

Study design. The study design specified that creek chub would be collected at several locations with known DDT concentrations in sediments. The fish would be analyzed for body burdens of DDT, and the relationship between DDT levels in the sediments and in the creek chub would be established. The fish DDT concentrations would be used to evaluate the DDT threat to piscivorous birds feeding on the fish at each location. Using the DDT concentrations measured in fish that correspond to a LOAEL and NOAEL for adverse effects in birds, the corresponding sediment contamination levels would be determined. Those sediment DDT levels then could be used to derive a cleanup level that would reduce threats of eggshell thinning to piscivorous birds.

The study design for measuring DDT residue levels in creek chub specified that 10 creek chub of the same size and sex would be collected at each location and that each creek chub be at least 20 grams, so that individuals could be analyzed. In addition, at one location, QA/QC requirements dictated that an additional 10 fish be collected. In this example, it was necessary to verify in the field that sufficient numbers of creek chub of the specified size were present to meet the tissue sampling requirements. In addition, the stream conditions needed to be evaluated to determine what fish sampling techniques would work best at the targeted locations.

The study design and methods for benthic macroinvertebrate collection followed the Rapid Bioassessment Protocol (RBP) manual for level three evaluation (U.S. EPA, 1989). Benthic macroinvertebrate samples were co-located with sampling for fish tissue residue levels so that one set of co-located water and sediment samples for analytic chemistry could serve for comparison with both tissue analyses.

The study design also specified that the hazard quotient (HQ) method would be used to evaluate the effects of DDT on the kingfisher during risk characterization. To determine the HQ, the estimated daily dose of DDT consumed by the kingfishers is divided by a LOAEL of 1.1 mg/kgBW-day for kestrels. To estimate the DDT dose to the kingfisher, the DDT concentrations in the chub is multiplied by the fish ingestion rate for kingfishers and divided by the body weight of kingfishers. This dose is adjusted by the area use factor. The area use factor corresponds to the proportion of the diet of a kingfisher that would consist of fish from the contaminated area. The area use factor is a function of the home range size of kingfishers relative to the area of contamination. The adjusted dose is compared to the LOAEL. A HQ of greater than one implies that impaired reproductive success in kingfishers due to site contamination is likely, and an HQ of less than one implies impacts due to site contaminants are unlikely (see text Section 2.3 for a description of HQs).

STEP 5: FIELD VERIFICATION OF STUDY DESIGN

A field assessment was conducted and several small fish collection techniques were used to determine which technique was the most effective for capturing creek chub at the site. Collected chub were examined to determine the size range available and to determine if individuals could be sexed.

Seine netting the areas targeted indicated that the creek chub might not be present in sufficient numbers to provide the necessary biomass for chemical analyses. Based on these findings, a contingency plan was agreed to (SMDP), which stated that both the creek chub and the longnosed dace (*Rhinichthys cataractae*) would be collected. If the creek chub were collected at all locations in sufficient numbers, those samples would be analyzed and the dace would be released. If sufficient creek chub could not be collected but sufficient longnosed dace could, the longnosed dace would be analyzed and the creek chub released. If neither species could be collected at all locations in sufficient numbers, then a mix of the two species would be used; however, for any given site only one species would be analyzed. In addition, at one location, preferably one with high DDT levels in the sediment, sufficient numbers of approximately 20 gram individuals of both species would be collected to allow comparison (and calibration) of the accumulation between the two species. If necessary to meet the analytic chemistry needs, similarly-sized individuals of both sexes of creek chub would be pooled. Pooling two or more individuals would be necessary for the smaller dace. The risk assessment team decided that the fish samples would be collected by electro-shocking. Field notes for all samples would document the number of fish per sample pool, sex, weight, length, presence of parasites or deformities, and other measures and might help to explain any anomalous data.

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