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CHEMICAL RISK ASSESSMENT

Selected Federal Agencies' Procedures, Assumptions, and Policies

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Abstract
As used in public health and environmental regulation, risk assessment is the systematic, scientific description of potential adverse effects of exposures to hazardous substances or situations. It is a complex but valuable set of tools for federal regulatory agencies, helping them to identify issues of potential concern, select regulatory options, and estimate the range of a forthcoming regulations benefits. For example, the Environmental Protection Agency (EPA) used risk assessment information in a 1998 final rule to conclude that disinfection byproducts (e.g., chloroform) in drinking water could cause as many as 9,300 bladder cancer cases a year, and that a 24-percent reduction in those byproducts could result in monetized health benefits of about $4 billion.1 However, risk assessments are also sometimes controversial, as evidenced by the fact that the disinfection byproduct rule was successfully challenged in court over whether the agency used the best scientific evidence available in support of certain assumptions.2 Given the significant yet controversial nature of risk assessments, it is important that policymakers understand how risk assessments are conducted, the extent to which risk estimates produced by different agencies and programs are comparable, and the reasons for differences in agencies risk assessment approaches and results.

Subject Terms

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Abbreviations

ADI	acceptable daily intake
AWQC	ambient water quality criteria
BAF	bioaccumulation factor
BAT	best available technology
CAA	Clean Air Act
CAAA	Clean Air Act Amendments
CEPPO	Chemical Emergency Preparedness and Prevention Office
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CSFII	Continuing Survey of Food Intakes by Individuals
CWA	Clean Water Act
DES	diethylstilbestrol
DOT	Department of Transportation
ED	effective dose
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
FAA	Federal Aviation Administration
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FHWA	Federal Highway Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
FRA	Federal Railroad Administration
FTA	Federal Transit Administration
GHS	globally harmonized system
HAZMAT	hazardous materials
HHS	Department of Health and Human Services
HMIS	Hazardous Materials Information System
HPV	high production volume
IRIS	Integrated Risk Information System
ISO	International Organization for Standardization
LED	lowest effective dose
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
MACT	maximum achievable control technology
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MEI	maximally exposed individual
MLE	maximum likelihood estimate

NAAQS	national ambient air quality standards
NAS	National Academy of Sciences
NCTR	National Center for Toxicological Research
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRC	National Research Council
OAQPS	Office of Air Quality Planning and Standards
OAR	Office of Air and Radiation
OERR	Office of Emergency and Remedial Response
OHMS	Office of Hazardous Materials Safety
OHMT	Office of Hazardous Materials Technology
OPP	Office of Pesticide Programs
OPPT	Office of Pollution Prevention and Toxics
OPPTS	Office of Prevention, Pesticides and Toxic Substances
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste
OW	Office of Water
PBPK	physiologically based pharmacokinetic
PEL	permissible exposure limit
PMN	premanufacture notification
POD	point of departure
RCRA	Resource Conservation and Recovery Act
RfC	reference concentration
RfD	reference dose
RSC	relative source contribution
RSPA	Research and Special Programs Administration
SAR	structure-activity relationship
SARA	Superfund Amendments and Reauthorization Act
SDWA	Safe Drinking Water Act
SOPs	standard operating procedures
STEL	short-term exposure limit
TI	tolerable intake
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UCL	upper confidence limit
UN	United Nations
USCG	United States Coast Guard
USDA	United States Department of Agriculture

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Accountability * Integrity * Reliability

United States General Accounting Office
Washington, D.C. 20548

August 6, 2001

The Honorable W. J. (Billy) Tauzin
Chairman, Committee on Energy and Commerce
House of Representatives

The Honorable Paul E. Gillmor
Chairman, Subcommittee on Environment
and Hazardous Materials
Committee on Energy and Commerce
House of Representatives

As used in public health and environmental regulation, risk assessment is the systematic, scientific description of potential adverse effects of exposures to hazardous substances or situations. It is a complex but valuable set of tools for federal regulatory agencies, helping them to identify issues of potential concern, select regulatory options, and estimate the range of a forthcoming regulation's benefits. For example, the Environmental Protection Agency (EPA) used risk assessment information in a 1998 final rule to conclude that disinfection byproducts (e.g., chloroform) in drinking water could cause as many as 9,300 bladder cancer cases a year, and that a 24-percent reduction in those byproducts could result in monetized health benefits of about $4 billion.[1] However, risk assessments are also sometimes controversial, as evidenced by the fact that the disinfection byproduct rule was successfully challenged in court over whether the agency used the best scientific evidence available in support of certain assumptions.[2] Given the significant yet controversial nature of risk assessments, it is important that policymakers understand how risk assessments are conducted, the extent to which risk estimates produced by different agencies and programs are comparable, and the reasons for differences in agencies' risk assessment approaches and results.

[1]"National Primary Drinking Water Regulations: Disinfectants and Disinfection Byproducts" (63 FR 69390, Dec. 16, 1998). The Food and Drug Administration published a related rule on disinfection byproducts in bottled water on March 28, 2001 (66 FR 16858).

[2]*Chlorine Chemistry Council v EPA*, 206 F.3d 1286 (D.C. Cir. 2000). In March 2001, EPA announced that it would propose a new assessment for chloroform, the disinfection byproduct that was the subject of the dispute, using an approach based upon different assumptions.

You asked us to provide information on selected federal agencies' risk assessment procedures and the similarities and differences in how the agencies' personnel are directed to conduct risk assessments. As you requested, our review focused on the human health and safety (and, to a lesser extent, ecological) risk assessment procedures of the following four agencies with primary responsibility for regulating or managing risks from potential exposure to chemicals: (1) EPA; (2) the Food and Drug Administration (FDA) within the Department of Health and Human Services (HHS); (3) the Occupational Safety and Health Administration (OSHA) within the Department of Labor; and (4) the Department of Transportation's (DOT) Research and Special Programs Administration (RSPA). These agencies regularly conduct chemical risk assessments in support of regulatory activities and/or illustrate the diversity of risk assessment procedures. Our primary objectives were to identify and describe (1) the general context for the agencies' chemical risk assessment activities; (2) what the agencies view as their primary procedures for conducting risk assessments; (3) what the agencies view as their major assumptions or methodological choices in their risk assessment procedures; and (4) the agencies' procedures or policies for characterizing the results of risk assessments. In addressing each of these objectives, we also identified similarities and differences between and within the agencies. To the extent feasible, we were also asked to identify as part of the third objective, (a) at what stages of the risk assessment process the assumptions are used, (b) the reasons given for their selection, (c) their likely effects on risk assessment results, and (d) how they compare to the assumptions and choices used by other agencies or programs in similar circumstances.

We addressed these objectives by reviewing agencies' general guidance documents or, if there were no such documents, specific examples of agencies' risk assessment procedures. We also reviewed previous reports on agencies' procedures, interviewed agency officials, and provided detailed descriptions of the relevant procedures to agency officials for their review and comment. Our review focused on chemical risk assessments in selected agencies, and therefore did not cover all types of risk assessments or even all agencies or programs that conduct chemical risk assessments. Also, our review did not evaluate how the selected agencies' procedures and policies are applied in individual risk assessments, or how risk assessment results are used in making regulatory decisions (risk management). We provided a draft of this report to five risk assessment experts to ensure technical accuracy. We also provided a draft to officials in each of the four agencies for their review and comment. The comments

that we received from both the experts and the agencies are reflected in the "Agency Comments and Our Evaluation" section of this letter. We conducted this review between February 2000 and March 2001 in accordance with generally accepted government auditing standards. Details of our scope and methodology are presented in appendix I.

Results in Brief

The context in which chemical risk assessments are conducted plays an important role in determining what type of assessments federal regulatory agencies perform and why certain approaches are used. The statutory and legal context determines the general focus and goals of an agency's risk assessment activities and also may shape how risk assessments for those activities are supposed to be conducted. The specific tasks and purposes for which an agency will use the results of a particular risk assessment determine the questions that the assessment needs to address and its scope and level of detail. For example, risk assessments used by OSHA to set occupational health standards must demonstrate that a significant risk exists and that the proposed standard would reduce that risk. However, in different contexts, FDA and EPA might use risk assessment procedures to estimate the dose of a chemical that people could consume daily without harmful effect, and not necessarily need to estimate the actual risk associated with exposure to that chemical. In other words, the focus of federal agencies' "risk" assessments can sometimes be characterized more accurately as safety assessment (i.e., estimating an exposure level below which no significant risk will occur) rather than as risk assessment (i.e., simply describing the likelihood of a risk).

All four of the agencies included in our review have standard procedures for conducting risk assessments involving chemical agents, although the agencies vary in the extent to which they have documented their procedures in written guidance. There are more similarities than differences in the overall chemical risk assessment procedures developed by three of the agencies—EPA, FDA, and OSHA. These agencies' procedures generally follow four-step process recommended by the National Academy of Sciences (NAS) of hazard identification, dose-response assessment, exposure assessment, and risk characterization. However, there are variations both among and within the agencies in the details of those steps, particularly during the exposure assessment step because agencies' regulatory authorities regarding chemical agents tend to vary according to the kinds or sources of exposure. The risk assessment procedures in DOT's RSPA are not based on the NAS four-step process because of the particular regulatory context in which RSPA operates.

Instead, a classification system that is harmonized with international agreements defines what is to be considered a hazardous material for transportation purposes according to the general physical characteristics of the material (e.g., whether it is explosive, flammable, or toxic). RSPA's analyses of risks then focus on identifying the potential circumstances under which unintentional releases of hazardous materials could occur during transit (e.g., due to transportation accidents) and assessing their consequences and probability of occurrence.

Assumptions are an unavoidable part of risk assessment because science cannot always provide definitive answers to questions raised at various stages of an assessment. Agency guidelines and officials we contacted during our review identified a large number and wide variety of assumptions that may be used, in the absence of adequate information, during the first three steps of a risk assessment. The agencies frequently indicated that particular assumptions were chosen on the basis of their evaluation of available scientific information, precedents established in prior assessments, or policy decisions related to the agencies' regulatory missions or mandates. In about half of the assumptions and methodological choices identified, the agencies described their likely effects on risk assessment results, most commonly (particularly at EPA and FDA) indicating that they were precautionary in nature.[3] Agencies use precautionary assumptions to ensure that a risk assessment will not underestimate risks. Consequently, they have the effect of raising the agencies' estimates of risk, compared to less precautionary options, and potentially lowering the chemical doses or exposure levels at which agencies might take regulatory action. Precautionary assumptions are particularly common in the agencies' procedures for initial screening risk assessments, when the primary task is to determine whether a risk might exist and more detailed analysis is needed. Agency guidelines and related documents indicate that subsequent assessments should involve more rigorous analyses and fewer precautionary assumptions. There are both similarities and differences in the assumptions and methods identified by EPA, FDA, and OSHA. RSPA, given its focus on analyzing transportation accident scenarios rather than chemical toxicity, uses different

[3]These are also referred to as "conservative" or "public-health conservative" assumptions. For consistency, we use the term precautionary throughout this letter. However, in the technical appendices on individual agencies we use the terms expressed in agency documents or by agency officials.

assumptions and methods because it tends to deal with different analytical issues.

Both EPA and DOT have written, agencywide risk characterization policies that emphasize clear, complete, and transparent disclosure of the data, methods, assumptions, and limitations of their risk assessments. The policies also encourage agency personnel to characterize their risk estimates in terms of ranges or distributions rather than simply providing a single point estimate of risks. Both agencies also encourage the use of peer review to obtain the views of other scientists and experts on the agencies' risk assessments. Although FDA and OSHA do not have written risk characterization policies, officials of those agencies said that in practice they tend to emphasize comprehensive characterizations of risk assessment results, discussions of limitations and uncertainties, and disclosure of the data and analytic methodologies on which the agencies relied.

The complexity and diversity of risk assessment policies, procedures, assumptions, and other choices affecting risk estimates underscore the importance of transparency in both individual risk assessments and agencies' general guidance documents. That transparency is particularly important with regard to disclosing why certain data, methods, and default assumptions are selected, and under what conditions the agency would depart from its default assumptions or methods. Prudent use of risk assessment results in formulating public policy requires policymakers to be aware of the assumptions and methods used in the preparation of the assessments.

Background

Risk assessments are conducted to estimate whether and/or how much damage or injury can be expected from exposures to a given risk agent and to assist in determining whether these effects are significant enough to require action, such as regulation. The effects of concern can be diseases such as cancer, reproductive and genetic abnormalities, workplace injuries, or various types of ecosystem damage. The risk agent analyzed in an assessment can be any number of things, including chemicals, radiation, transportation systems, or a manufacturing process. The product of a risk assessment is a quantitative and/or qualitative statement regarding the probability that an exposed population will be harmed and to what degree.

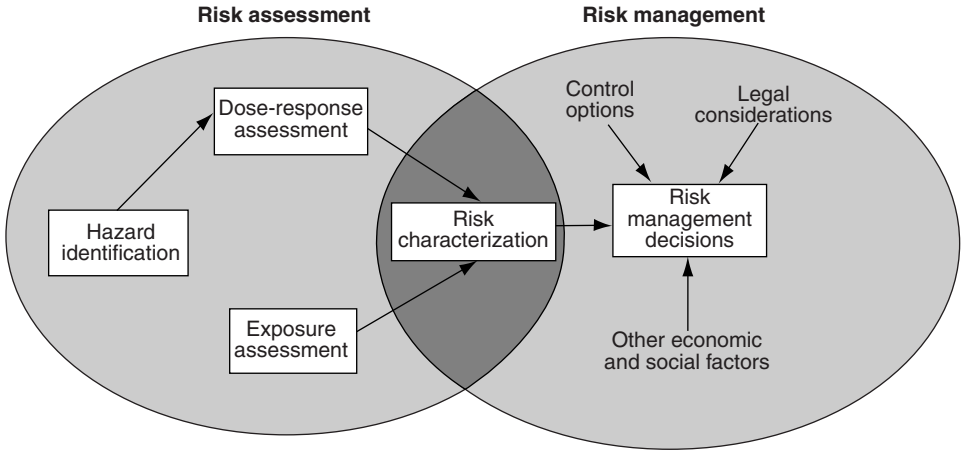
Risk assessment, particularly quantitative risk assessment, is a relatively new discipline, developed in the first half of the 20th century to establish

various health and safety codes and standards. The role of risk assessment in the regulatory process was accelerated by the enactment of various health, safety, and environmental statutes in the early 1970s. The development of chemical risk assessment procedures has traditionally followed two different tracks—one for assessments of cancer risks and another for assessments of noncancer risks. The procedures associated with cancer risks have historically assumed that there is no "threshold" below which an agent would not cause adverse effects. In contrast, procedures for assessments of noncancer risks were largely developed under the assumption that there is such a threshold—that exposures up to a certain level would not be expected to cause harm.

In 1983, NAS identified four steps in the risk assessment process: (1) *hazard identification* (determining whether a substance or situation could cause adverse effects), (2) *dose-response assessment* (determining the relationship between the magnitude of exposure to a hazard and the probability and severity of adverse effects), (3) *exposure assessment* (identifying the extent to which exposure actually occurs), and (4) *risk characterization* (combining the information from the preceding analyses into a conclusion about the nature and magnitude of risk).[4] This paradigm, originally intended to address assessments of long-term health risks, such as cancer, has become a standard model for conducting risk assessments, but is not the only model (e.g., different models are used for ecological risk assessments). According to NAS, the results of the *risk assessment* process should be conceptually distinguished from how those results are used in the *risk management* process (e.g., the decision on where to establish a particular standard). As illustrated by figure 1, the risk management decision considers other information in addition to the risk characterization.

[4]*Risk Assessment in the Federal Government: Managing the Process* (commonly referred to as the "Red Book"), National Research Council of the National Academy of Sciences (National Academy Press, 1983).

Figure 1: Typical Sequence of Risk Assessment and Risk Management Processes



Source: EPA Office of Research and Development.

More recent reports have updated and expanded on these original concepts. In 1996, NAS urged risk assessors to update the original concept of risk characterization as a summary added at the end of a risk assessment.[5] Instead, the report suggested that risk characterization should be a "decision-driven" activity directed toward informing choices and solving problems and one that involves decision makers and other stakeholders from the very inception of a risk assessment. In this updated view, the nature and goals of risk characterization are dictated by the goals of the risk management decisions to be made. Similarly, the Presidential/Congressional Commission on Risk Assessment and Risk Management (hereinafter referred to as the Presidential/Congressional Commission) recommended in 1997 that the performance of risk assessments be guided by an understanding of the issues that will be important to risk management decisions and to the public's understanding of what is needed to protect public health and the environment.[6]

[5]*Understanding Risk: Informing Decisions in a Democratic Society*, National Research Council of the National Academy of Sciences (National Academy Press, 1996).

[6]*Risk Assessment and Risk Management in Regulatory Decision-Making*, The Presidential/Congressional Commission on Risk Assessment and Risk Management, (Final Report, Volume 2, 1997).

Data on Chemical Health Effects and Exposures Are Limited

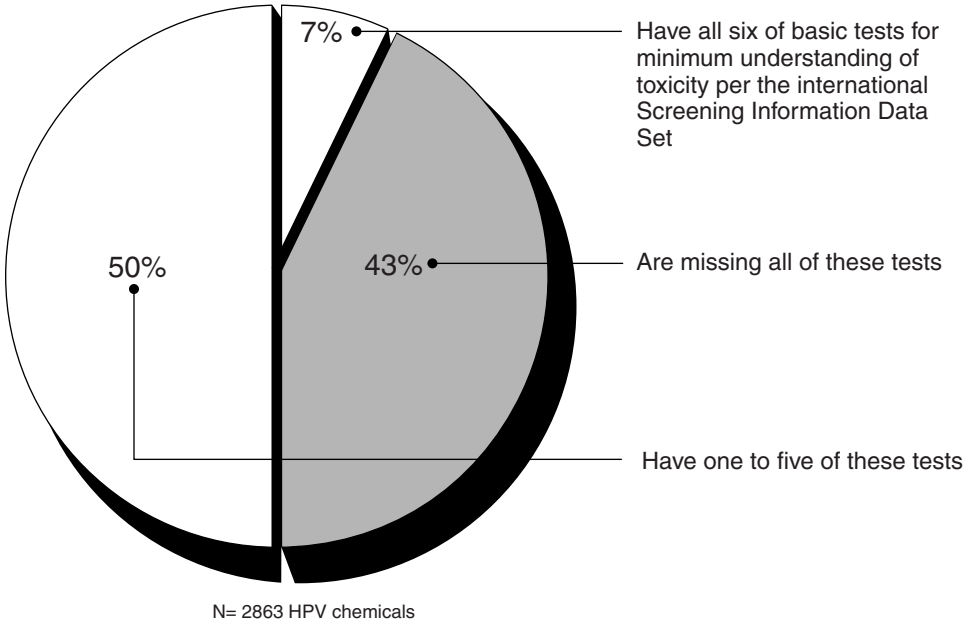
Substantial numbers and amounts of chemical substances and mixtures are produced, imported, and used in the United States. For example, there are over 70,000 commercial chemicals in EPA's Toxic Substances Control Act (TSCA) Chemical Substances Inventory, and the agency receives about 1,500 petitions each year requesting the approval of new chemicals or new uses of existing chemicals.[7] However, there is relatively little empirical data available on the toxicity of most chemicals and the extent to which people or the environment might be exposed to the chemicals. For example, we previously reported that EPA's Integrated Risk Information System (IRIS), which is a database of the agency's consensus on the potential health effects of chronic exposure to various substances found in the environment, lacks basic data on the toxicity of about two-thirds of known hazardous air pollutants.[8] Furthermore, to the extent that data on health effects are available, the data are more often from toxicological studies involving animal exposures than from epidemiological studies involving human exposures. As a consequence, chemical risk assessments must rely often on extrapolation from animal studies and are quite different from risk assessments that use epidemiological studies or actuarial data (such as accident statistics).

[7]Excluding polymers (which are considered unlikely to present significant risk concerns), EPA's TSCA inventory identified about 15,000 chemicals produced or imported at levels above 10,000 pounds per year. There are also other categories of chemical substances (such as drugs, cosmetics, food additives, and pesticides) that are exempt from TSCA but subject to control under other federal statutes. The number of chemicals actually in commerce varies as new chemicals are added and other chemicals are withdrawn.

[8]*Major Management Challenges and Program Risks: Environmental Protection Agency* (GAO/OCG-99-17, Jan. 1999).

The limited nature of information on chemical toxicity was illustrated in a 1998 EPA report on the data that were publicly available on approximately 3,000 high-production-volume (HPV) chemicals.[9] For each of these chemicals, EPA examined the available data corresponding to six basic tests that have been internationally agreed to as necessary for a minimum understanding of a chemical's toxicity.[10] As shown in figure 2, the agency concluded that the full set of basic toxicity data was available for only about 200 (7 percent) of the chemicals, and that 43 percent of the chemicals did not have publicly available data for any of the six tests.

Figure 2: Full Toxicity Data Is Available for Only a Small Portion of High-Production-Volume Chemicals



Source: EPA, *Chemical Hazard Data Availability Study: What Do We Really Know About the Safety of High Production Volume Chemicals?* (April 1998).

[9]High-production-volume chemicals are those imported or produced at volumes of more than 1 million pounds per year. Note that, for regulatory approval purposes, some offices within EPA have access to confidential business information on commercial chemicals and pesticides that would not be reflected in this study of "publicly available" toxicity data.

[10]The six tests are acute toxicity, chronic toxicity, developmental/reproductive toxicity, mutagenicity, ecotoxicity, and environmental fate. Collectively, these tests are known as the Screening Information Data Set program.

There are also significant gaps in the available data on the extent to which people are exposed to chemicals. For example, last year we reviewed federal and state efforts to collect human exposure data on more than 1,400 naturally occurring and manmade chemicals considered by HHS, EPA, and other entities to pose a threat to human health.[11] We reported that, taken together, HHS and EPA surveys measured the degree of exposure in the general population for only 6 percent of those chemicals. Even for those chemicals that were measured, information was often insufficient to identify smaller population groups at high risk (e.g., women, children, and the elderly).

Uncertainty Contributes to Controversy about Chemical Risk Assessment

There is an ongoing debate about the appropriate application of risk assessment in federal regulation. In 1990, Congress mandated that a commission be formed to "make a full investigation of the policy implications and appropriate uses of risk assessment and risk management in regulatory programs under various Federal laws to prevent cancer and other chronic human health effects which may result from exposure to hazardous substances." The Presidential/Congressional Commission published its final report in 1997, and noted that often "the controversy arises from what we don't know and from what risk assessments can't tell us."[12] NAS has also emphasized that science cannot always provide definitive answers to questions raised during the course of conducting a risk assessment, so risk assessors must use assumptions throughout the process that reflect professional judgments and policy choices.[13]

[11]*Toxic Chemicals: Long-Term Coordinated Strategy Needed to Measure Exposures in Humans* (GAO/HEHS-00-80, May 2, 2000). See also *Environmental Information: EPA Needs Better Information to Manage Risks and Measure Results* (GAO-01-97T, Oct. 3, 2000).

[12]*Framework for Environmental Health Risk Management*, The Presidential/Congressional Commission on Risk Assessment and Risk Management, (Final Report, Volume 1, 1997), p. 23.

[13]See *Risk Assessment in the Federal Government: Managing the Process* (1983) and *Science and Judgment in Risk Assessment* (1994).

One focus of the risk assessment debate has been agencies' use of precautionary assumptions and analytical methods. The term "precautionary" refers to the use of methods and assumptions that are intended to produce estimates that should not underestimate actual risks. Some critics of federal risk assessment practices believe agencies use assumptions that are unjustifiably precautionary in the face of new scientific data and methods, thereby producing estimates that overstate actual risks. The critics contend that this effect is compounded when multiple precautionary assumptions are used. Others, however, criticize agency practices for not being precautionary enough in the face of scientific uncertainties, failing, for example, to adequately account for the synergism of exposures to multiple chemicals or the risks to persons most exposed or most sensitive to a particular toxic agent.[14] Other observers, including NAS, have expressed concerns about whether the agencies' procedures and assumptions are sufficiently transparent, thereby providing decision makers and the public with adequate information about the scientific and policy bases for agencies' risk estimates as well as the limitations and uncertainties associated with those estimates.

[14]Proposals have been introduced in Congress regarding this issue. For example, H.R. 199, proposed in the 106th Congress, would have required the EPA Administrator to evaluate, among other things, environmental health risks to vulnerable subpopulations (e.g., children, pregnant women, and the elderly) and to ensure that all EPA standards protect such subpopulations with an adequate margin of safety.

We have discussed these issues in several previous reports. For example, in 1993, we noted that EPA used precautionary assumptions throughout the process that it used to assess risk at Superfund hazardous waste sites, and that the agency had been criticized for overstating risk by combining precautionary estimates.[15] In September 2000, we reported on EPA's use of precautionary "safety factors" pursuant to the Food Quality Protection Act of 1996.[16] In October 2000, we said that three factors influenced EPA's use of precautionary assumptions in assessing health risks: (1) the agency's mission to protect human health and safeguard the natural environment, (2) the nature and extent of relevant data (e.g., animal versus human studies), and (3) the nature of the health risk being evaluated (e.g., cancer versus noncancer risks).[17]

Context for Agencies' Chemical Risk Assessments Is Important

The context in which chemical risk assessments are conducted plays an important role in determining what type of assessments federal regulatory agencies perform and why certain approaches are used. Two dimensions seem particularly important to understanding the context for an agency's chemical risk assessment activities: (1) the general statutory and legal framework underlying the agency's regulation of chemicals and (2) how the agency plans to use the risk assessment information.[18] The statutory and legal framework determines the general focus and goals of an agency's chemical risk assessment activities and also can shape how risk assessments for those activities are supposed to be conducted. The specific tasks and purposes for which an agency will use the results of a particular risk assessment determine the questions that the assessment needs to address and the scope and level of detail of the assessment.

[15]*Superfund: Risk Assessment Process and Issues* (GAO/T-RCED-93-74, Sept. 30, 1993).

[16]*Children and Pesticides: New Approach to Considering Risk Is Partly in Place* (GAO/HEHS-00-175, Sept. 11, 2000).

[17]*Environmental Protection Agency: Use of Precautionary Assumptions in Health Risk Assessments and Benefits Estimates* (GAO-01-55, Oct. 16, 2000).

[18]Other contextual factors, such as the data limitations and scientific uncertainty, are also important. On a practical level, the availability of resources (e.g., staff, schedule, funding, data) also affects the scope and level of detail that an agency can provide in any given risk assessment. However, such factors are either so broadly applicable or so case specific that they do not distinctively characterize the risk assessment procedures of an agency or program.

Statutory and Legal Framework

A diverse set of statutes addresses potential health, safety, and environmental risks associated with chemical agents. These statutory mandates generally focus on different types and sources of exposure to chemicals, such as consumption of pesticide residues in foods, occupational exposures to chemicals, or inhalation of toxic air pollutants. Therefore, different agencies (and different offices within those agencies) have distinctive concerns regarding chemical risks. For example, each major program office within EPA (e.g., the Office of Air and Radiation or the Office of Water) is responsible for addressing the risk-related mandates of one or more statutes (e.g., the Clean Air Act, the Clean Water Act, or the Safe Drinking Water Act). Also, international agreements provide important legal context for transportation risk assessment activities. For example, criteria for classifying dangerous chemicals in transportation have been internationally harmonized through the United Nations' Recommendations on the Transport of Dangerous Goods.

The legal framework underlying chemical regulation influences both the extent to which risk assessment is needed for regulatory decision making and how risk assessments are supposed to be conducted. Some statutes require regulatory decisions to be based solely on risk (considering only health and environmental effects), some require technology-based standards (such as requiring use of the best available control technology), and still others require risk balancing (requiring consideration of risks, costs, and benefits). For example, section 112 of the Clean Air Act (CAA), as amended, has a technology-based mandate requiring the use of the maximum achievable control technology to control emissions of hazardous air pollutants. A risk assessment is not needed to determine such technology, but would be used to evaluate residual risks that remain after that technology is in use. Some statutes also place the primary responsibility for conducting risk assessments and compiling risk-related data for a particular chemical or source of exposure to chemical agents with industry, states, or local entities, rather than with the federal regulatory agencies. For example, industry petitioners have the primary responsibility to provide the data needed to support registration and tolerances from EPA for their pesticides, including information on the toxicological effects of the pesticides.[19]

[19] Registration involves the licensing of pesticides for sale and use in agriculture and extermination. No chemical may be sold in the United States as a pesticide without such registration, which establishes the conditions of legal use. Pesticide tolerances are the concentrations permitted to remain in or on food, as it is available to the consumer.

Statutes can also affect risk assessment by specifically defining what will be considered a hazard, directing the agency to take certain methodological steps, or specifying the exposure scenario of regulatory concern. For example, in response to the "Delaney Clause" amendments to the Federal Food, Drug, and Cosmetic Act, FDA identifies any food additive for which an adequately conducted animal cancer study indicates that the additive produces cancer in animals as a carcinogen under the conditions of the study. No further corroboration or weight-of-evidence analysis is required. The Food Quality Protection Act of 1996 requires EPA to add an additional 10-fold safety factor to protect infants and children when deriving standards for allowable pesticide residues in foods, unless reliable data show that a different factor will be safe. Provisions in the Occupational Safety and Health Act focus OSHA's risk assessments on estimating the risks to workers exposed to an agent for a working lifetime.

However, in most cases the statutes simply provide a general framework within which the agencies make specific risk assessment assumptions and methodological choices. For example, section 109 of the CAA requires EPA to set national ambient air quality standards that in the judgment of the EPA Administrator—and allowing for an "ample margin of safety"—are requisite to protect the public health.[20] EPA risk assessors translate that general requirement into specific risk assessment assumptions and methods (e.g., whether to assume a threshold or no-threshold relationship between dose and response at low doses).

Use of Risk Assessment Results

The specific purpose or task of an assessment determines the kinds of risk information needed for the agency to make its risk management decisions, and can significantly influence the scope and level of detail required of a risk assessment. For example,

- If the agency's task is to set a specific health-based standard (e.g., a national air quality standard), a rigorous and detailed estimate of risks at particular exposure levels might be required.
- If the agency's task is to decide whether to approve the production and use of commercial chemicals or pesticides, risk assessors may initially focus on potential upper-bound exposures (e.g., assuming that a chemical agent will be used at the maximum level permitted by law or

[20] An ambient air quality standard is a national target for an acceptable concentration of a specific pollutant in air.

focusing on individuals who consume the greatest amounts of a food containing residues of the agent at issue). If such upper-bound estimates exhibit no cause for concern, the agency may have no need to complete a more comprehensive and refined risk assessment.
- A decision on whether to add or remove a chemical from the list of potential hazards might focus the risk assessors on determining whether the potential risk is above or below a specific threshold level, such as the risk of 1 extra cancer case over the lifetime of 1 million people.

The influence of the specific regulatory task at hand is illustrated by a method commonly used by agencies for risk assessments of noncancer health effects. Agencies such as EPA and FDA have historically attempted to identify a dose level of a chemical associated with no observed adverse effect level (NOAEL) in animal experiments—or the lowest observed adverse effect level (LOAEL) in the study, if every tested dose exhibited some effect.[21] They then divided that NOAEL or LOAEL dose by multiple "safety" or "uncertainty" factors to account for the possibility that humans may be more sensitive to the chemical than animals and other uncertainties. This procedure is designed to identify a dose not likely to result in harm to humans, not to provide an explicit quantitative estimate of the risks associated with a given chemical. In other words, sometimes the focus of federal agencies' "risk" assessments could more accurately be described as a safety assessment (i.e., estimating a "safe" level of exposure to chemical agents or a dose below which no significant risk is expected to occur) rather than a risk assessment (i.e., estimating the actual risks associated with exposures to chemical agents).

Implications of Contextual Differences

Because of contextual differences, the risk assessment procedures used, the resulting risk estimates (and regulatory actions based upon those estimates), and even whether a substance would be subject to risk assessment, can vary among different agencies and programs within the same agency. The following examples illustrate how contextual differences affect the conduct of risk assessments.

- Because regulation of certain wastes may be impractical or otherwise undesirable, regardless of the hazards that the waste might pose,

[21]FDA often determines a no observed effects level (NOEL) rather than a NOAEL because many significantly altered, standard toxicological endpoints are assumed to be adverse to animals and/or humans even in the absence of data affirming that assumption.

Congress and EPA exempted certain materials (e.g., agricultural or mining and mineral processing wastes) from the definitions of hazardous wastes. If a material meets one of the categories of exemptions, it cannot be identified as a hazardous waste even if it otherwise meets the criteria for listing as a hazardous waste. For example, according to EPA's *RCRA Orientation Manual*, wastes generated in raw material, product storage, or process (e.g., manufacturing) units are exempt from EPA's hazardous waste regulation while the waste remains in such units. However, OSHA might assess and regulate risks associated with such materials as part of its mission to protect the health of employees in the workplace.

- FDA and EPA both assess potential human health risks associated with ingestion of chemical substances. If a substance is being assessed by FDA as a food additive and results from any adequate study indicate that the substance produces cancer in animals, FDA labels that additive as a carcinogen without considering other scientific evidence (per the Delaney clause of the Federal Food, Drug, and Cosmetic Act, as amended). However, when assessing the risks associated with consumption of residues from animal drugs (FDA) and pesticides (EPA) the agencies may need to consider many scientific studies in determining whether and under what conditions an agent might cause cancer or other adverse health effects in humans.
- EPA's risk assessments of commercial chemicals under TSCA vary depending on whether the chemical at issue is "existing" or "new." For EPA to control the use of an existing chemical, the agency must make a legal finding that the chemical *will* present an unreasonable risk to human health or the environment. EPA said this standard requires the agency to have conclusive data on risks associated with that particular chemical. By comparison, newly introduced chemicals can be regulated based on whether they *may* pose an unreasonable risk, and this finding of risk can be based on data for structurally similar chemicals, not just data on that particular chemical. Because industrial chemicals in commerce were "grandfathered" under TSCA into the inventory of existing chemicals more than 20 years ago, without considering whether they were hazardous, there are situations in which existing chemicals might not be controlled while, at the same time, EPA would act to control a new chemical of similar or less toxicity.
- Within EPA's Office of Water, risk assessments vary depending on whether the assessment is done to establish drinking water standards or standards for ambient water (e.g., bodies of water such as lakes and rivers). Risk assessments for drinking water standards focus solely on human health effects, but assessments used to establish ambient water

quality criteria consider both human health and ecological effects. Even when considering just the human health risks, an important difference between the ambient and drinking water risk assessments is an additional focus for ambient water on exposures to contaminated water through consumption of contaminated fish or shellfish. This additional factor is a primary reason for potential differences in drinking water and ambient water risk estimates and standards for the same chemical.

Appendices II through V describe the relevant contextual factors for each of the four selected agencies in greater detail.

Agencies' Risk Assessment Procedures Share Common Features, But Substantive Differences Also Exist

All four of the agencies included in our review have standard procedures for conducting risk assessments, although the agencies vary in the extent to which their procedures are documented in written guidance. In general, there are more similarities than differences across EPA, FDA, and OSHA procedures, because each of these agencies generally follows the four-step NAS risk assessment process. The procedures address the same basic questions regarding hazard identification, dose-response assessment, and exposure assessment. The specific analytical methods and approaches in those procedures are also very similar (e.g., extrapolating from animal study data to model dose-response relationships in humans, and generally using different procedures for assessing cancer and noncancer risks). The most substantive differences across and within these agencies are related to exposure assessment, reflecting the diversity in the agencies' regulatory authorities regarding chemical agents across different kinds or sources of exposure. For example, both OSHA and EPA consider methylene chloride (also known as dichloromethane) to be a probable human carcinogen. However, this same chemical can be identified as a significant hazard by one agency in one exposure setting (OSHA for purposes of assessing health risks associated with occupational exposures) but as a low hazard by another agency in a different setting (EPA for purposes of Superfund hazard ranking screening).[22] RSPA, although sharing a concern over identifying risks and analyzing their consequences and probabilities of

[22] EPA has taken other actions regarding exposures to methylene chloride. For example, EPA requires that releases of methylene chloride of 1,000 pounds or more be reported to the federal government. EPA also has guidelines on how much of this chemical people can be exposed to without harming their health (e.g., EPA recommends that children not drink water that contains more than 13.3 parts of methylene chloride per million parts of water for longer than 1 day or with more than 1.5 parts per million for longer than 10 days).

occurrence, has a different structure to its risk assessments than the other three agencies because of its focus on risks associated with unintentional releases of hazardous materials during transportation. In general, all four agencies are incorporating more complex analytical models and methods into their risk assessment procedures. However, some of the advanced models require much more detailed information than may be currently available for many chemicals.

Risk Assessment Procedures at EPA

EPA has extensive written internal risk assessment procedures. For example, EPA has agencywide guidelines, policy memoranda, and handbooks covering the following aspects of risk assessment:

- carcinogen risk assessment,
- neurotoxicity risk assessment,
- reproductive toxicity risk assessment,
- developmental toxicity risk assessment,
- mutagenicity risk assessment,
- health risk assessment of chemical mixtures,
- exposure assessment,
- ecological risk assessment,
- evaluating risk to children,
- use of probabilistic analysis in risk assessment,
- use of the benchmark dose approach in health risk assessment, and
- use of reference dose and reference concentration in health risk assessment.

EPA also has numerous program-specific guidelines and policy documents, such as the Risk Assessment Guidance for Superfund series and a set of more than 20 science policy papers and guidelines from the Office of Pesticide Programs in response to the Food Quality Protection Act of 1996. Many of the agency's guidance documents are draft revisions to earlier documents or procedures or draft guidance on new issues that have not previously been addressed by EPA. Although such drafts are not yet final, official statements of agency policies or procedures, they may better represent the current practice of risk assessment in EPA than earlier "final" documents.

EPA generally follows the NAS four-step risk assessment process. (The major exception is the agency's Chemical Emergency Preparedness and Prevention Office, which follows a different set of procedures because of its focus on risks associated with accidental chemical releases from fixed facilities. See app. II for a discussion of this office's risk assessment procedures.) EPA's risk assessment activities generally involve both the program offices (e.g., the Office of Air and Radiation or the Office of Solid Waste) and the Office of Research and Development (ORD), which is the principal scientific and research arm of the agency. ORD often does risk assessment work for EPA program offices that focuses on the first two steps in the four-step NAS process—hazard identification and dose-response assessment—in particular, the development of "risk per unit exposed" numbers.[23] Preparation of the final two steps in the process—exposure assessment and risk characterization—tends to be the responsibility of the relevant program offices. Several programs, for example, frequently use a single hazard assessment, but for different exposure scenarios. There are, however, exceptions to this generalization. For example, ORD carries out all steps for highly complex, precedent-setting risk assessments, such as those for dioxin and mercury. There are also instances when EPA program offices carry out all four steps of the process. In some situations, EPA agencywide procedures also depart slightly from the NAS paradigm. For example, when assessing noncancer health effects, EPA's normal practice is to do hazard identification in conjunction with the analysis of dose-response relationships, rather than as distinct steps. According to EPA's guidelines, this is because the determination of a hazard is often dependent on whether a dose-response relationship is present. In the case of ecological risk assessments, EPA's guidelines suggest a three-step process consisting of (1) problem formulation, (2) analysis, and (3) risk characterization, rather than the four-step process used for health risk assessments.

[23]ORD also manages EPA's IRIS database that contains agency-consensus information on human health effects that may result from exposure to various chemicals in the environment.

EPA has identified several new directions in its approach to exposure assessment. First is an increased emphasis on total (aggregate) exposure to a particular agent via all pathways. EPA policy directs all regulatory programs to consider in their risk assessments exposures to an agent from all sources, direct and indirect, and not just from the source that is subject to regulation by the office doing the analysis.[24] Another area of growing attention is the consideration of cumulative risks, when individuals are exposed to many chemicals at the same time. The agency is also increasing its use of probabilistic modeling methods to analyze variability and uncertainty in risk assessments and provide better estimates of the range of exposure, dose, and risk to individuals in a population than are provided by single point estimates. EPA's guidance on probabilistic methods outlines standards that exposure data prepared by industry or other external analysts must meet to be accepted by EPA.

Risk Assessment Procedures at FDA and OSHA

FDA and OSHA also generally follow the NAS risk assessment paradigm, but neither FDA nor OSHA had written internal guidance specifically on conducting risk assessments at the time of our review. However, both agencies' standard procedures are well documented in the records of actual risk assessments and in summary descriptions that have appeared in scientific and professional literature. In addition, FDA has published volumes of guidance on risk assessments for use by external parties affected by the agency's regulations (e.g., animal drug manufacturers seeking FDA approval for their products). According to FDA officials, the documents are meant to represent the agency's current thinking on the scientific data and studies considered appropriate for assessing the safety of a product, and sometimes include detailed descriptions of the risk assessment methods deemed appropriate to satisfy FDA's requirements under various statutory provisions. However, these guidelines do not preclude the use of alternative procedures by either FDA or external parties.

The responsibility for conducting risk assessments in FDA is divided among the agency's program offices. For example, FDA's Center for Food

[24]The Presidential/Congressional Commission noted that, traditionally, risk assessments have largely focused on assessing the risks of just one chemical in one medium at a time. Although some EPA offices, such as the Office of Pesticide Programs and Office of Water, conduct more comprehensive risk assessments, the Commission pointed out that few other regulatory agencies consider exposures or risks comprehensively, and EPA often does not do so because of resource or statutory limitations.

Safety and Applied Nutrition (CFSAN) is responsible for assessing risks posed by food additives and contaminants, while the Center for Veterinary Medicine (CVM) is responsible for assessing risks posed by animal drug residues in food. In addition, FDA's National Center for Toxicological Research conducts scientific research to support the agency's regulatory needs, including research aimed at understanding the mechanisms of toxicity and carcinogenicity and at developing and improving risk assessment methods. FDA officials said that there are variations in the risk assessment approaches used among the agency's different product centers and, in some cases, within those centers. In general, those variations are traceable to differences in factors such as the substances being regulated, the nature of the health risks involved (particularly carcinogens versus noncarcinogens), and whether the risk assessment is part of the process to review and approve a product before it can be marketed and used (premarket) or part of the process of monitoring risks that arise after a product is being used (postmarket). For example, risk assessments by CFSAN's Office of Food Additive Safety and Office of Nutritional Products, Labeling and Dietary Supplements are mandatory for new dietary ingredients (and are used for premarket review of such ingredients) but discretionary for other food (and are associated with postmarket review). A unique characteristic of the hazard identification phase of risk assessment in FDA is that, by statute, if there is an adequate study that indicates a food additive can cause cancer in animals, that additive is labeled as a carcinogen under the conditions of the study. No additional corroboration or weight-of-evidence analysis is required in such cases, and there is no need to complete the other three risk assessment steps before proceeding to a regulatory decision. FDA's CVM is permitted to allow the use of carcinogenic drugs in food-producing animals under the DES proviso of the Federal Food, Drug, and Cosmetic Act, as amended, provided that "no residue of such drug will be found."

OSHA's Directorate of Health Standards Programs is primarily responsible for conducting the agency's chemical risk assessments. Such assessments focus specifically on the potential risks to workers associated with exposures to chemicals in an occupational setting. In contrast to agencies regulating environmental exposures to toxic substances, OSHA frequently has relevant human data available on occupational exposures. Even when the agency assesses risks based on animal data, OSHA said that the workplace exposures of concern are often not far removed from levels tested in the animal studies. Therefore, OSHA's risk assessments do not extrapolate as far beyond the range of observed toxicity as might be necessary to characterize environmental exposure risks. OSHA's risk assessment procedures have also evolved to consider data from advanced physiologically based pharmacokinetic (PBPK) models on the relationship between administered doses and effective doses (i.e., the amounts that actually reach a target organ or tissue).[25] However, PBPK models are complicated and require substantial data, which may not be available for most chemicals. OSHA therefore developed a set of 11 criteria to judge whether available data are adequate to permit the agency to rely on PBPK analysis in place of administered exposure levels when estimating human equivalent doses.

[25]Pharmacokinetics is the study of the absorption, distribution, metabolism, and elimination of chemicals in humans and animals. It is the basis for developing what are believed to be more realistic and accurate models of the movement and interactions of a chemical with blood, tissues, and organs once it enters the body, including consideration of the body's ability to repair damage caused by a chemical.

Risk Assessment Procedures at RSPA

The applicable risk assessment guidance for RSPA is generally documented within broader DOT-wide guidance on conducting regulatory analyses and also in materials describing the agency's Hazardous Materials Safety Program. Because of the particular regulatory context in which it operates, RSPA does not apply the NAS four-step paradigm for risk assessment used by EPA, FDA, and OSHA. RSPA is primarily concerned with potential risks associated with the transportation of hazardous materials. In particular, it is concerned with short-term or acute health risks due to relatively high exposures from unintentional release of hazardous materials. For its purposes, RSPA identifies chemicals as hazardous materials according to a regulatory classification system that is harmonized with internationally recognized criteria and EPA-defined hazardous substances. This classification system defines the type of hazard associated with a given material according to chemical, physical, or nuclear properties (e.g., whether it is an explosive, a flammable liquid, or a poisonous substance) that can make it dangerous in or near transporting conveyances. Therefore, a chemical's toxicity is only one of its characteristics of concern to RSPA, rather than being the primary focus of analysis as in assessments of the other three agencies. The risk analyses by RSPA focus on identifying the potential circumstances under which unintentional releases of hazardous materials could occur during transit (e.g., due to transportation accidents) and assessing their consequences and probability of occurrence. Analysis of different modes (e.g., via truck, rail, or aircraft) and routes of transportation is an important component of RSPA's consequence and probability analyses.[26] Through DOT databases, directly relevant data on the incidence and severity of hazardous materials transportation accidents are available to assist RSPA in identifying and analyzing hazard scenarios.

Appendices II through V provide more detailed descriptions of the standard procedures for chemical risk assessments in each of the four selected agencies.

[26]Assessment and regulation of risks associated with substances transported by bulk marine carriers are the responsibility of the United States Coast Guard.

Agencies' Risk Assessment Procedures Often Include Precautionary Assumptions and Methods

Assumptions and methodological choices are an integral and inescapable part of risk assessment. They are often intended to address uncertainty in the absence of adequate scientific data. However, those assumptions and methods may also reflect policy choices, such as how to address variability in exposures and effects among different individuals and populations, or particular contextual requirements. To the extent that the four agencies identified the specific reasons for selecting their major assumptions or methods, they most often attributed their choices to an evaluation of available scientific data, the precedents established in prior risk assessments, or policy decisions related to their regulatory missions. Agencies' statements regarding the likely effects of their preferred assumptions and methods most often addressed the extent to which the default options would be considered precautionary. Some of the major assumptions and methodological choices of EPA, FDA, and OSHA address similar issues and circumstances during the risk assessment process, especially regarding assessment of a chemical's toxicity.

Agencies' Assumptions and Methodological Choices Vary

Agency procedural guidelines and officials we contacted during our review identified a large number and wide variety of major assumptions and methodological choices that they might use when conducting chemical risk assessments, in the absence of information that would indicate the particular assumption or method is not valid in a given case. Some of these assumptions and methodological choices were very broad (e.g., the common assumption that, in the absence of evidence to the contrary, substances that produce adverse health effects in experimental animals pose a potential threat to humans). Other assumptions and choices were more specific, covering particular details in the analytical process (e.g., identifying the preferred options for extrapolating high dose-response relationships to low doses). EPA and OSHA identified some of their choices as the default assumptions and methods of their agencies. FDA officials said that their agency does not require the use of specific default assumptions or risk assessment methods, but there are assumptions and methods that typically have been used as standard choices in FDA risk assessments. Although assumptions are also needed in RSPA's risk assessments, RSPA officials said that they do not have any default assumptions. Instead, they said that their assumptions are specific to, and must be developed as part of, each risk assessment.

Appendices II through V present detailed information on some of what the agencies identified as their major assumptions and methodological choices

in chemical risk assessments. The tables illustrate both the number and variety of assumptions that agencies may use when conducting those assessments.

The following sections summarize information that was available from the four agencies' procedures and related documents on (a) when the agencies employ major assumptions and methods, (b) their reasons for selecting these options, (c) the likely effects on risk assessment results of these options, and (d) how they compare to the assumptions and choices used by other agencies or programs in similar circumstances. In some cases the agencies' documents did not contain this information, but there is no requirement that the agencies do so. Also, the reason for using a particular assumption and its effect on risk assessment results can vary on a case-by-case basis, and therefore might not be addressed in general risk assessment guidance. Nevertheless, both NAS and the Presidential/Congressional Commission recommended greater transparency regarding the procedures, assumptions, and results of agencies' risk assessments. Also, as will be discussed more fully later in this report, the agencies' own risk characterization policies and practices emphasize the value of such transparency in communicating information about risk assessment procedures and results. Recent regulatory reform proposals considered by Congress have had provisions requiring transparency in the use of assumptions.[27]

When Assumptions and Methods Are Used

As previously mentioned, NAS and the Presidential/Congressional Commission have both emphasized that science cannot always provide definitive answers to questions raised during a risk assessment. For example, in 1983, NAS identified at least 50 points during the course of a cancer risk assessment when choices had to be made on the basis of professional judgment, not science. EPA's guidelines similarly point out that, because there is no instance in which a set of data on an agent or exposure is complete, all risk assessments must use general knowledge and policy guidance to bridge data gaps. Except in the case of RSPA, default or standard assumptions and methods may be used by agencies to

[27]For example, S. 746, proposed in the 106th Congress, provided that when a risk assessment involves a choice of assumptions the agency must (1) identify significant assumptions and their scientific and policy bases, (2) explain the basis for any choices among assumptions, and (3) describe reasonable alternative assumptions not selected that would have had a significant effect on the results of the assessment.

address these gaps in knowledge, and to encourage consistency in the efforts of agencies' risk assessors to address such basic issues as:

- uncertainty in the underlying data, model parameters, or state of scientific understanding of how exposure to a particular chemical could lead to adverse effects;
- variability in the potential extent of exposure and probability of adverse effects for various subgroups or individuals within the general population;[28] and
- statutory requirements (and the related general agency missions) to be protective of public health and the environment (e.g., to set standards with "an adequate margin of safety").

However, agency risk assessors have considerable flexibility regarding whether to use particular assumptions and methods, even when the agency has default or standard options. For example, EPA stated that its revised guidelines for carcinogen risk assessment were intended to be both explicit and more flexible than in the past concerning the basis for making departures from defaults, recognizing that expert judgment and peer review are essential elements of the process. The Executive Director of ORD's Risk Assessment Forum pointed out that, although EPA's guidelines always permitted such flexibility, without detailed guidance on departing from default assumptions there had been a tendency for analysts to not do so. He also stated that when determining whether to use a default, the decision maker must consider available information on an underlying scientific process and agent-specific data, and that scientific peer review, peer consultation workshops, and similar processes are the principal ways of determining the strength of thinking and the general acceptance of these views within the scientific community. FDA officials emphasized that their agency does not presume that there is a "best way" of doing a risk assessment and does not require the use of a specific risk assessment protocol or of specific default assumptions, but they are continually updating procedures and techniques with the goal of using the "best available science."

[28]There is a conceptual difference between uncertainty and variability. Uncertainty is a property of a lack of knowledge and may be reduced through study and additional information. Variability is a property of a system or population (e.g., every person has different physical characteristics) and can only be understood, not reduced, through further study. See Adam Finkel, "A Second Opinion on an Environmental Misdiagnosis," *New York University Environmental Law Journal*, Volume 3 (1995), p. 299.

Agencies identified assumptions and methodological choices throughout the risk assessment process, and each of the first three steps in the process can have its own set of issues and choices that risk assessors need to address. During hazard identification, agencies must make choices about which types of data to use and what types of adverse effects and evidence will be considered in their analyses. For example, risk assessors need to decide whether data on benign tumors should be used along with data on malignant tumors as the basis for quantitative estimates of cancer risks, or whether only data on malignant tumors should be used. During dose-response assessment, agencies may need to make assumptions when extrapolating effects from animals to humans (e.g., how to determine equivalent doses across different species). In particular, choices among assumptions and methods are needed when estimating dose-response relationships at doses that are much lower than those used in the scientific studies that provided the data for quantitative analysis. During exposure assessments, assumptions might be needed to address issues such as when exposures occur (e.g., in infancy or childhood versus as an adult), how long exposures last (e.g., short versus long term and continuous versus episodic), differences in exposures and effects for the population as a whole versus those affecting subpopulations and individuals, and questions about the concentration and absorption of chemical agents. Assumptions about human behavior also affect the relative likelihood of different exposure scenarios. For example, in assessing children's residential exposures to a pesticide, risk assessors might need to make assumptions about how long children play in a treated area, the extent to which they are wearing clothing, and potential hand-to-mouth exposure to treated soil, among other factors.

Why Particular Assumptions and Methods Are Selected

Agencies generally indicated that they use their major assumptions and methodological choices in risk assessments when professional judgments or policy choices must substitute for scientific information that is not available or is inconclusive. We examined risk assessment guidance documents and procedures in the four agencies to determine whether the agencies stated a specific scientific or policy basis for their choices, as recommended by NAS and the Presidential/Congressional Commission. In approximately three-quarters of the choices that we reviewed, the agencies provided at least some rationale for the use of particular assumptions or methods. The reasons most commonly cited were (1) an evaluation of available scientific data, (2) the precedents established in prior risk assessments, and (3) policy decisions related to their regulatory mandates. In some instances, the agencies cited more than one reason in support of their choices. For example, officials from FDA's Center for Veterinary Medicine said they assume that an adult weighs 60 kilograms when converting an acceptable daily intake (ADI) to an intake level of residues in food because of historical precedent and because this assumption should protect women, growing adolescents, and the elderly.[29]

[29]According to FDA officials, if there is a need to convert an ADI (expressed as milligrams per kilogram body weight per day) to an intake level (expressed as the number of milligrams of an additive that would be acceptable on a daily basis), they multiply the ADI by the assumed weight of a person. Officials from FDA's Center for Food Safety and Applied Nutrition said they assume values of 60 kilograms for adults and 15 kilograms for children, based on historical precedents which were based on population-based surveys.

Of the three reasons, the agencies most often cited their evaluation of available scientific evidence as a reason for selecting particular assumptions or analytical methods. For example, one of the default assumptions in EPA's carcinogen risk assessment guidance is that positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans. EPA cited scientific research supporting this assumption, such as the evidence that nearly all agents known to cause cancer in humans are carcinogenic in animals in tests with adequate protocols. Other EPA guidelines stated that, in general, a threshold is assumed for the dose-response curve for agents that produce developmental toxicity. EPA's guidelines noted that this assumption is based on the known capacity of the developing organism to compensate for or repair a certain amount of damage at the cellular, tissue, or organ level. OSHA cited scientific evidence and the views of the Office of Science and Technology Policy on chemical carcinogenesis (the origin or production of a tumor) to support its choice to combine data on benign tumors with the potential to progress to malignancies with data on malignant tumors occurring in the same tissue and the same organ site.[30]

[30]The National Science and Technology Policy, Organization, and Priorities Act of 1976 created the Office of Science and Technology Policy within the Executive Office of the President to provide advice to the President on issues relating to science and to coordinate federal efforts in science and technology.

Even when basing a choice upon available scientific studies and data, professional judgment may still be required regarding which particular method or assumption to choose among competing alternatives. The scientific evidence might show a range of assumptions or methods that provide plausible results and may, in specific cases, vary in terms of which one best fits the available evidence. For example, different mathematical models can be used for estimating the low-dose effects of exposure to suspected carcinogens. A basic problem for risk assessors is that, while the results produced by different models may be similar at higher doses, the estimates can vary dramatically at the low doses that are of concern to agency regulators. One study of 5 dose-response models showed that all of the models produced essentially the same dose-response curves at higher doses, but the models' estimates differed by 3 or 4 orders of magnitude (values 1,000 to 10,000 times different) at lower doses.[31] Because the mechanism of carcinogenesis is not sufficiently understood, none of the mathematical procedures for extrapolation has a fully adequate biological basis.[32] Furthermore, because of the limitations in the ability of toxicologic or epidemiologic studies to detect small responses at very low doses, dose-response relationships in the low-dose range are practically unknowable.

Agencies can encounter similar problems in attempting to determine how much of a chemical will produce the same effect in humans that was observed in animals. An interagency group of federal scientists that studied this issue noted that, although many alternatives had been developed for such cross-species scaling, and despite considerable study and debate, "no alternative has emerged as clearly preferable, either on empirical or theoretical grounds."[33] The group noted further that the various federal agencies conducting chemical risk assessments therefore developed their own preferences and precedents, and this variation "stands among the chief causes of variation among estimates of a chemical's potential human risk, even when assessments are based on the same data." For purposes of consistency in federal risk assessments, the group recommended a method intermediate between the two methods most

[31] See "Criteria for Evidence of Chemical Carcinogenicity," Interdisciplinary Panel on Carcinogenicity, *Science* 225 (1984), pp. 682-687.

[32] See, for example, *General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals*, DHHS/FDA/CVM (revised July 1994).

[33] "Draft Report: A Cross-Species Scaling Factor for Carcinogen Risk Assessment Based on Equivalence of mg/kg$^{3/4}$/Day," 57 FR 24152 (June 5, 1992). No final report has been issued.

commonly used by federal agencies, but reiterated that methodologies in use "have not been shown to be in error."

Other reasons cited by the agencies for selecting assumptions or methods included the precedents established in prior risk assessments and policy decisions related to their regulatory missions and mandates. For example, FDA officials said that their practice of using the most sensitive species and sex when calculating the ADI of animal drug residues in food was based on historical precedents dating back to at least 1954. In other instances, FDA said that its use of precautionary assumptions was based on the agency's statutory responsibility to ensure to a "reasonable certainty" that the public will not be harmed. Similarly, EPA guidelines pointed out that the default assumptions used in the agency's risk assessments were chosen to be health protective because EPA's overall goal is public health protection. For example, EPA's neurotoxicity guidelines said that a choice to use the most sensitive animal species to estimate human risk "provides a conservative estimate of sensitivity for added protection to the public."

Effects of Agencies' Assumptions and Methods on Risk Estimates

The agencies provided information in their guidelines on the likely effects of using particular assumptions or methods in about half of the examples that we reviewed. When that information was provided, it was usually in the context of whether and to what extent the agencies' choices could be considered precautionary. In a number of cases, EPA and FDA characterized their assumptions and methods as precautionary in that they were intended to avoid underestimating risks in the interest of protecting public health. Such assumptions tend to raise an agency's estimate of risk and lower the levels of exposure that are of regulatory concern. Precautionary assumptions and methodological choices were a common component of programs that have "tiered" approaches for conducting risk assessments (e.g., EPA's Superfund and pesticides programs). In these tiered risk assessment approaches, agencies move from initial rough screening efforts to increasingly more refined and detailed levels of analyses. The initial screening assessments will typically involve very precautionary "upper-bound" or even "worst-case" assumptions to determine whether there is cause for concern. Successive tiers of assessment, if deemed necessary, are characterized in agency documents as more detailed and focused assessments that require more extensive data and rigorous analysis. For example, EPA indicated that its screening assessments might well use precautionary upper-bound point estimates of exposures (e.g., that a chemical is used on 100 percent of the eligible crop and at the maximum permissible limit). However, subsequent tiers of

assessments might refine those estimates through the use of probability distributions of exposure parameters or the use of monitoring data on actual exposures, when feasible.

OSHA and RSPA also use precautionary assumptions in certain parts of their risk assessment procedures. However, these agencies identified few of their risk assessment assumptions and methods as precautionary. In fact, OSHA sometimes selected assumptions or methods that it explicitly characterized as less precautionary than those used by other agencies in similar circumstances. For example, OSHA stated that its standard approach to low-dose extrapolation can be much less precautionary than EPA's or FDA's approaches because it tends to use central estimates of potency rather than upper-bound confidence limits. OSHA officials also noted that the algorithm they use is less precautionary because it may lead to models that are sublinear at low doses.

The effect on risk estimates of using any one assumption is likely to be less significant than that of applying a series of assumptions while conducting a risk assessment, particularly if the assessment is compounding a string of largely precautionary assumptions. As we previously pointed out, assumptions and choices may be needed at many points during each step of an agency's analysis. The agency's policy may well be to use precautionary choices at most, if not all, of those points, if adequate information is not available to indicate that the precautionary choice is invalid in a specific case. The potential for such a string of precautionary assumptions is illustrated by the set of standard choices identified by FDA for risk assessments of carcinogenic animal drug residues in foods consumed by humans.

1. Regulation is based on the target tissue site exhibiting the highest potential for cancer risk for each carcinogenic compound.

2. If tumors are produced at more than one tissue site, the minimum concentration of the compound that produced a tumor is used.

3. Cancer risk estimates are generally based on animal bioassays, using upper 95-percent confidence limits of carcinogenic potency.[34]

4. Low-dose extrapolation is done using a nonthreshold, conservative, linear-at-low-dose procedure (i.e., assuming that there is no dose that would not cause cancer and that effects vary in proportion to the amount of the dose).

5. It is assumed that the carcinogenic potency in humans is the same as that in animals.

6. The concentration of the residue in the edible product is at the permitted concentration.

7. Consumption is equal to that of the 90th percentile consumer.

8. All marketed animals are treated with the carcinogen.

9. In the absence of information about the composition of the total residue in edible tissue, assume that the entire residue is of carcinogenic concern.

FDA's description of its risk assessment procedures acknowledged that these assumptions "result in multiple conservatisms" and stated that some of these choices are likely to overestimate risk by an unknown amount (although the fourth assumption could also underestimate risk by an order of magnitude). However, the agency also said that these assumptions are prudent because of the uncertainties involved and cited its statutory responsibility to ensure to a reasonable certainty that the public will not be harmed. It is important to keep in mind that the primary purposes for preparing such assessments are to identify safe concentration levels in edible tissues and residue tolerances (the amount permitted to remain on food) for postmarket monitoring rather than to produce a general estimate of the risk posed by use of the animal drug.

[34] Bioassay refers to the use of living organisms to measure the effect of a risk agent or condition—for example, a test for carcinogenicity in laboratory animals that includes near-lifelong exposure to the agent being tested.

Comparison of Agencies' Assumptions

Agency documents very rarely made direct comparisons of their assumptions and methodological choices to those used by other agencies, and there is no requirement that they do so. Our review indicated that EPA, FDA, and OSHA risk assessment procedures have many basic assumptions in common—for example, that one can use results of animal experiments to estimate risks to humans, and that most potential carcinogens do not have threshold doses below which adverse effects would not occur. There are other default or standard assumptions and models in the three agencies' risk assessment procedures that are similar, but not identical. For example, all three agencies employ a linear mathematical model for low-dose extrapolation (in the absence of information indicating that a linear model is inappropriate in a particular case). However, the agencies prefer different options in the details of fitting such models, such as the point of departure to low doses. EPA and FDA also consider similar, but not identical, sets of uncertainty or safety factors when using the NOAEL approach for noncancer risk assessments. Finally, as the discussion above regarding low-dose extrapolation illustrates, there are also instances in which the agencies use different assumptions in similar circumstances.

Table 1 compares and contrasts some of the risk assessment assumptions or analytical methods identified in the guidelines or other descriptive documents of EPA, FDA, and OSHA for use under similar circumstances.[35] (Note that, for comparability, the examples in table 1 all focus on carcinogen risk assessments based on animal studies, but the agencies' major assumptions and methods are not limited to only carcinogen risk assessments. Note also that the "circumstances" listed in the table also include that the assumption or method would be used in the absence of data to the contrary.)

[35]RSPA is not included in this table because it uses a different process for risk assessments, and its assessments do not focus on the carcinogen risk assessment issues highlighted in the table. However, RSPA's risk assessment methods are similar to EPA's Chemical Emergency Preparedness and Prevention Office, which also focuses primarily on short-term risks associated with accidental releases of chemicals.

Table 1: Comparison of Selected Major Assumptions or Methods Used in EPA, FDA, and OSHA Risk Assessments

Circumstance	EPA	FDA	OSHA
Which species/sex to use in animal studies.	Use most sensitive species/sex.	Use most sensitive species/sex.	Use most sensitive species/sex for tumor sites appropriate for routes of exposure experienced by workers.
Whether to include data on benign tumors in a cancer assessment.	Include data on benign tumors if they have the capacity to progress to the malignancies with which they are associated. Benign tumors that are not observed to progress to malignancy are assessed on a case-by-case basis.	Include data on benign tumors if they have the capacity to progress to the malignancies with which they are associated. Benign tumors that are not observed to progress to malignancy are assessed on a case-by-case basis.	Combine data on benign tumors with the potential to progress to malignancies with data on malignant tumors occurring in the same tissue and the same organ site.
Preferred cancer low-dose extrapolation method if a mathematical model is used.	Default depends on the agent's mode of action. For example, if mode is not understood or believed to be linear, a linear approach is recommended. When data supports a nonlinear mode of action, the default changes to a margin of exposure analysis.	Use a no-threshold, linear extrapolation method.	Use a particular no-threshold, linear approach known as the "maximum likelihood estimate in the Crump-Howe reparameterization of the multistage model." (This particular approach may lead to models that are sublinear at low doses.)
Point of departure in preferred approach to low-dose extrapolation (i.e., the data point from which the agency extrapolates to lower, unobserved dose-response relationships).	Use the lower 95-percent limit of the doses that are estimated to cause a 10-percent response (i.e., an effect in 10 percent of exposed subjects). (This dose is referred to as the LED_{10}.)	Use data at the upper 95-percent confidence limit.	According to agency officials, OSHA does not use a point of departure. OSHA tends to use central estimates of potency, such as the maximum likelihood estimate of the parameterized dose-response function.
Preferred method for cross-species scaling of equivalent doses (i.e., how the agency converts data from doses given to one species, such as rats in a toxicological study, to doses presumed to have an equivalent effect on another species, such as humans).	For oral exposure, recommends use of a scaling factor of body weight to the ¾ power.	Recommends use of scaling factor of body weight to the ¾ power. (However, risk assessors may also use the default of body weight scaling.)	Assumes that equivalent doses scaled by body weight would lead to equivalent risks. (However, it may in the future move to ¾ -power scaling.)

Source: GAO analysis

There appears to be some convergence in the agencies' risk assessment assumptions in at least one area where there had been significant differences—their methods for cross-species dose scaling. In the absence of adequate information on differences between species, EPA's standard practice in carcinogenic risk assessments had been to scale daily administered doses by body surface area, whereas FDA's and OSHA's standard practice had been to scale doses by body weight. Recently, the agencies have either adopted, or consider as one of their options, the expression of doses in terms of daily amount administered per unit of body weight to the ¾ power.[36]

All four of the agencies included in our review have also been incorporating more complex analytical methods and models into their risk assessment procedures. Some of these methods (such as the use of probabilistic analyses to provide distributions of exposure parameters) help to address issues of uncertainty and variability in risk assessments and lessen the need for some precautionary assumptions. Other advances, such as the use of PBPK models, can provide better insights into how and to what extent a chemical might produce adverse effects in humans. One outcome of the integration of these methods into agencies' procedures is a diminishing of the traditional distinction between cancer and noncancer risk assessment methods. EPA, in particular, has noted that it is less likely to consider cancer and noncancer endpoints in isolation as it develops and incorporates more advanced scientific methods to measure and model the biological events leading to adverse effects. According to EPA, the science of risk assessment is moving toward a harmonization of the methodology for cancer and noncancer assessments.

The use of newer, more complex models and methods also opens up a new range of choices and assumptions in the analysis—along with the potential for risk estimates to diverge because of the different assumptions that might be used. For example, in its methylene chloride final rule OSHA reported on the results of its analyses as well as risk assessments submitted to OSHA by other risk assessors.[37] Although most of the risk assessments used a linearized multistage model to predict risk, there were differences in the estimates produced by these assessments. OSHA

[36] Across the range of plausible values, the body weight approach is generally considered the least precautionary, surface area scaling the most precautionary, and (body weight)$^{3/4}$ the midpoint value.

[37]"Occupational Exposure to Methylene Chloride," 62 FR 1494 (Jan. 10, 1997).

pointed out that the differences in risk estimates were not generally due to the dose-response model used, but to whether the risk assessor used PBPK modeling to estimate target tissue doses and what assumptions were used in the PBPK modeling.

Appendices II through V present more detailed information on some of the major assumptions and methodological choices in each of the four selected agencies.

Risk Characterization Policies and Practices Emphasize Transparency

In the risk characterization step of a risk assessment, agencies bring together the results of the preceding analyses in the form of estimates and conclusions about the nature and magnitude of a potential risk. Agencies' risk characterizations play a crucial role in explaining to decision makers and other interested parties what the agency's risk assessors have concluded and on what basis they reached those conclusions. Both EPA and DOT have agencywide written policies on risk characterization that emphasize the importance of providing comprehensive and transparent characterizations of risk assessment results. Although FDA and OSHA do not have written risk characterization policies, officials of those agencies pointed out that, in practice, they also tend to emphasize comprehensive characterizations of risk assessment results, discussions of limitations and uncertainties, and disclosure of the data and analytic methodologies on which the agencies relied.

EPA's program offices are generally responsible for completing risk characterizations, and EPA's agencywide guidance on this issue includes a risk characterization policy, a guidance memorandum, and a handbook. EPA's policy stipulates that risks should be characterized in a manner that is clear, transparent, reasonable, and consistent with other risk characterizations of similar scope. EPA said that all assessments "should identify and discuss all the major issues associated with determining the nature and extent of the risk and provide commentary on any constraints limiting fuller exposition." EPA's policy documents also recommend that risk characterization should (1) bridge the gap between risk assessment and risk management decisions; (2) discuss confidence and uncertainties involving scientific concepts, data, and methods; and (3) present several types of risk information (e.g., a range of exposures and multiple risk descriptors such as high-end estimates and central tendencies). It is also EPA's policy that major scientifically and technically based work products related to the agency's decisions normally should be peer-reviewed.[38]

In its guidelines for carcinogen risk assessment, EPA also suggests preparing separate "technical" characterizations to summarize the findings of the hazard identification, dose-response assessment, and exposure assessment steps. The agency's risk assessors are then to use these technical characterizations to develop an integrative analysis of the whole risk case, followed by a less extensive and nontechnical summary intended to inform the risk manager and other interested readers. EPA identified several reasons for preparing separate characterizations of each analysis phase before preparing the final integrative summary. One is that different people often do the analytical assessments and the integrative analysis. The second is that there is very often a lapse of time between the conduct of hazard and dose-response analyses and the conduct of the exposure assessment and integrative analysis. Thus, according to EPA, it is necessary to capture characterizations of assessments as the assessments are done to avoid the need to go back and reconstruct them. Finally, several programs frequently use a single hazard assessment for different exposure scenarios.

[38] Peer review generally takes one of two forms: (1) internal peer review by a team of relevant experts from within EPA who have no other involvement with respect to the work product that is to be evaluated or (2) external peer review by a review team that consists primarily of independent experts from outside EPA.

DOT's policy principles regarding how the results of its risk or safety assessments should be presented are straightforward and encourage agency personnel to:

- make public the data and analytic methods on which the agency relied (for replication and comment);
- state explicitly the scientific basis for significant assumptions, models, and inferences underlying the risk assessment, and explain the rationale for these judgments and their influence on the risk assessment;
- provide the range and distribution of risks for both the full population at risk and for highly exposed or sensitive subpopulations and encompass all appropriate risk to health, safety, and the environment;
- place the nature and magnitude of risks being analyzed in context (including appropriate comparisons to other risks); and
- use peer review for issues with significant scientific dispute.

FDA does not have a written risk characterization policy, but FDA officials said that, in practice, the agency uses a standard approach that is similar to EPA's official policy. They said that FDA's general policy is to reveal the risk assessment assumptions that have the greatest impact on the results of the analysis, and to state whether the assumptions used in the assessment were conservative. FDA officials also said that their risk assessors attempt to show the implications of different distributions and choices (e.g., the results expected at different levels of regulatory intervention). FDA may employ probabilistic methods, such as Monte Carlo analysis, to provide additional information on the effects of variability and uncertainty on estimates of risk, and there are some differences in FDA risk characterization procedures depending on the products being regulated and the nature of the risks involved.[39]

Although OSHA does not have written risk characterization policies, in recent rules the agency emphasized (1) comprehensive characterizations of risk assessment results; (2) discussions of assumptions, limitations, and uncertainties; and (3) disclosure of the data and analytic methodologies on which the agency relied. The agency devoted considerable effort to addressing uncertainty and variability in its risk estimates. Such efforts

[39]Monte Carlo analysis involves a repeated random sampling from the distribution of values for each of the parameters in a calculation (such as average daily exposure) to derive a distribution of estimates of exposures for a population. According to FDA, because Monte Carlo modeling is a probabilistic technique that can use all the available data, it will result in more accurate estimates at upper percentiles of exposure.

included performing sensitivity analyses and providing estimates produced by alternative analyses and assumptions (including analyses by risk assessors outside of OSHA). In its risk characterizations, OSHA provided both estimates of central tendency and upper limits (such as the 95th percentile of a distribution).

Appendices II through V provide more detailed descriptions of the risk characterization policies or approaches of each of the four selected agencies.

Conclusions

Risk assessment is an important, but extraordinarily complex, element in federal agencies' regulation of potential risks associated with chemicals. The assessments can help agencies decide whether to regulate a particular chemical, select regulatory options, and estimate the benefits associated with regulatory decisions. Scientific studies in such areas as toxicology and epidemiology are often used to produce the information needed for risk assessment decisions. However, assessors frequently must produce estimates of risk without complete scientific information about the extent of exposures to potentially hazardous substances and the effects of those exposures on human health and safety or the environment. Therefore, professional judgment with regard to assumptions and methodological choices is an inherent part of conducting risk assessments. The appendices to this report identify many of the major assumptions and methods that can be used in risk assessments prepared for EPA, FDA, OSHA, and RSPA. The number and variety of those assumptions and methods illustrate the range of issues that risk assessors confront during the course of their analyses.

Although there were more similarities than differences in the general risk assessment procedures of three of the four agencies, there were also some notable differences in the agencies' specific approaches, methods, and assumptions. These differences can significantly affect the results and conclusions drawn from the assessments. Therefore, risk estimates prepared by different agencies, or by different program offices within those agencies, may not be directly comparable, even if the same chemical agent is the subject of the risk assessment. In some cases, the reasons for those differences are readily apparent, such as when agencies focus on different types of adverse effects (e.g., cancer versus noncancer) or different types and sources of exposure. For example, the same chemical (e.g., methylene chloride) might be identified as a significant hazard by one agency in one exposure setting (OSHA for occupational exposures) but as a low hazard

by another agency in a different setting (EPA for Superfund hazard ranking screening). In other cases, the reasons for different estimates may be more subtle and harder to discern within the many layers of analyses and professional judgments used to prepare the risk assessment.

Because of the range of assumptions and methods that are scientifically plausible in a given situation, the risk characterization phase of the risk assessment process takes on added importance. In their risk characterization policies or procedures, the four agencies acknowledge the importance of clearly communicating not only their conclusions about the nature and likelihood of a given risk but also disclosing (1) the assumptions, methods, data, and other choices that had the greatest impact on risk estimates; (2) why those choices were made; and (3) the effect that alternative choices would have had on the results of a risk assessment. Transparency is important with regard to both individual risk assessments and in agencies' general procedures regarding how the assessments should be conducted. Those procedures encourage consistency in how agencies conduct risk assessments and provide insights into agencies' decision making when analyzing risks. For example, frameworks delineated by EPA and OSHA for departing from certain default assumptions inform both agency personnel and external parties as to whether particular data or analyses are acceptable to the agency.

Our review focused on describing the framework for agencies' chemical risk assessments. We did not evaluate how that framework is applied in practice, or how risk assessment results affect risk management decisions by agencies and other policymakers. Nevertheless, our report highlights the value of policymakers and other interested parties becoming aware of the underlying risk assessment context, procedures, assumptions, and policies when using risk assessment data for risk management and other public policy decisions. For example, prudent use of risk data requires the user to be aware of the extent to which the data:

- represent estimates from screening assessments (which may rely heavily on precautionary assumptions) or estimates from subsequent, more rigorous assessments (which are likely to rely on more detailed and case-specific data and analyses);
- show the distribution of exposures and potential adverse effects across the population, including the extent to which the data address risks of the most exposed or sensitive subgroups of the population, or focus on only part of that distribution;

- were produced using directly relevant scientific data that were available or had to rely on general assumptions and models; and
- reflect the flexibility permitted in agencies' standard procedures or guidelines to depart from past precedent and default choices to use alternative assumptions and models, when appropriate.

In our review we also found that, although the underlying statutes specified the use of particular methods or assumptions in only three instances, the legal and situational context within which an agency is conducting a chemical risk assessment has a major effect on the specific focus, scope, and level of detail of the resulting assessment. Comparison of risk assessment estimates from different agencies and programs therefore requires careful consideration of these contextual differences.

Because the central purpose of our review was to describe the framework for selected agencies' chemical risk assessments, rather than to evaluate and critique how that framework is applied in practice, we are not making any recommendations in this report.

Agency Comments and Our Evaluation

At the end of our review, we sent a draft of this report to five experts in the field of risk assessment to ensure the technical accuracy of the report. The three experts who provided comments were (1) the Executive Director of the Presidential/Congressional Commission, (2) the individual who prepared the *Survey of Methods for Chemical Health Risk Assessment Among Federal Regulatory Agencies* for the Commission, and (3) an expert in risk assessment at Resources for the Future. The experts generally indicated that the report had no material weaknesses, but provided a number of technical suggestions that we incorporated as appropriate. For example, two of the reviewers suggested that the report's discussion of the NAS four-step risk assessment paradigm, although reflecting the definitions generally relied upon by federal agencies, should also identify an updated view regarding the concept of risk characterization. The updated view is that risk characterization should be a decision-driven activity performed as part of the risk management decision making process rather than a stand-alone activity at the end of a risk assessment. We included this perspective in the report's background section.

During our review, we obtained technical comments from officials in each of the four agencies on a draft of the appendices to this report, which we incorporated as appropriate. On June 18, 2001, we sent a draft of the full

report to the Secretaries of Health and Human Services, Labor, and Transportation, and the Administrator of EPA for their review and comment. None of the agencies provided formal comments on the report, but we received additional technical comments and suggestions from all four of the agencies, which we incorporated as appropriate.

As arranged with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days after the date of this report. At that time, we will send copies of this report to the Ranking Minority Member, House Committee on Energy and Commerce; the Ranking Minority Member, Subcommittee on Environment and Hazardous Materials, House Committee on Energy and Commerce; the Secretaries of Health and Human Services, Labor, and Transportation; and the Administrator of EPA. We will also make copies available to others on request.

If you have any questions concerning this report, please call me or Curtis Copeland at (202) 512-6806. Key contributors to this assignment were Timothy Bober and Aaron Shiffrin.

Victor S. Rezendes
Managing Director, Strategic Issues

Objectives, Scope, and Methodology

Scope and Objectives

As requested, our review focused on the chemical risk assessment procedures, assumptions, and policies of four federal agencies with responsibilities for regulating or managing risks from potential exposure to chemicals—the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) within the Department of Health and Human Services (HHS), the Occupational Safety and Health Administration (OSHA) within the Department of Labor, and the Department of Transportation's (DOT) Research and Special Programs Administration (RSPA—in particular the Office of Hazardous Materials Safety). Our specific objectives were to identify and describe (1) the general context for the agencies' chemical risk assessment activities; (2) what the agencies view as their primary procedures for conducting risk assessments; (3) what the agencies view as the major assumptions or methodological choices in their risk assessment procedures; and (4) the agencies' procedures or policies for characterizing the results of risk assessments. To the extent feasible, we were also asked to identify for the assumptions and choices identified in the third objective (a) at what stages of the risk assessment process they are used, (b) the reasons given for their selection, (c) their likely effects on risk assessment results, and (d) how they compare to the assumptions and choices used by other agencies or programs in similar circumstances.

Methodology

To address our objectives, we relied primarily on a detailed review and analysis of agencies' general guidance documents on chemical risk assessment or, if there were no guidance documents, reviews of specific examples of agency risk assessments. We supplemented that information with material from secondary source reports on risk assessment and interviews with agency officials. Among the secondary sources that we used were relevant reports by the Congressional Research Service, National Academy of Sciences (NAS), and the Presidential/Congressional Commission on Risk Assessment and Risk Management (hereinafter referred to as the Presidential/Congressional Commission). In particular, as a starting point for our review we used a report on federal agencies' chemical risk assessment methods that was prepared by Lorenz Rhomberg for the Presidential/Congressional Commission.[1] That report provided the baseline descriptions of some of the chemical risk assessment procedures at EPA, FDA, and OSHA.[2] We asked officials of those agencies to review Rhomberg's report to identify information that was still relevant to addressing the objectives of this report as well as information that they felt should be revised or added to reflect the agencies' current procedures.

There are several important limitations to our review. First, chemical risk assessment is just one of several types of risk assessment being conducted in federal agencies. Therefore, our review cannot be used to characterize other types of risk assessments (e.g., risks associated with radiation exposure). In fact, FDA officials considered risk assessments related to the human drug approval process to be outside the scope of our review because a completely different protocol is used in those assessments. However, limiting the scope of our review to chemical risk assessments makes comparisons among the agencies included more relevant and meaningful. Second, our review did not include all agencies or programs that conduct risk assessments involving chemicals. For example, we did not include the Consumer Product Safety Commission, which periodically assesses products with potential risks from chemicals. Nor did we include the Agency for Toxic Substances and Disease Registry, which prepares "health assessments" that closely resemble risk assessments but has no regulatory authority. We focused on the risk assessment procedures in four federal agencies that regularly conduct chemical risk assessments in

[1] *A Survey of Methods for Chemical Health Risk Assessment Among Federal Regulatory Agencies*, Lorenz Rhomberg (1996).

[2] RSPA was not included in the scope of Rhomberg's report.

support of regulatory activities and/or could illustrate the diversity of risk assessment procedures. However, the results of our review cannot be considered representative of chemical risk assessments in all federal agencies. Third, our review does not describe every chemical risk assessment procedure or assumption used by the agencies we reviewed. The material describing the agencies' procedures is both voluminous and extremely complex. The detailed information that we provide on agency assumptions is illustrative of the assumptions included in agencies' procedures, but not a compendium of all such assumptions. In addition, we concentrated primarily on the human health and safety risk assessment procedures of the four agencies and, to a lesser extent, on ecological risk assessment procedures. Fourth, this report describes agencies' general procedures and policies, but it is not a compliance review of how well those procedures and policies are applied with regard to individual assessments. The agencies' guidelines represent suggested procedures and are not binding, so the agencies' practices may justifiably vary from the general frameworks we describe. In practice, risk assessments do not follow a simple recipe or formula. Each assessment has unique issues or characteristics that require case-specific resolutions. Finally, this report does not address risk management issues—e.g., using the results of a risk assessment to determine what level of exposure to a risk agent represents an acceptable or an unacceptable risk and deciding what control options should be used.

We conducted this review between February 2000 and March 2001 in the Washington, D.C., headquarters offices of the selected agencies in accordance with generally accepted government auditing standards. We obtained technical comments on our descriptions of the agencies' procedures, assumptions, and policies in the appendices from knowledgeable agency personnel. We then provided the draft report to external experts in risk assessment, including the Center for Risk Analysis at the Harvard School of Public Health in Boston, MA; Resources for the Future in Washington, D.C.; the Executive Director of the Presidential/Congressional Commission; and Lorenz Rhomberg, the analyst who surveyed federal agencies' chemical risk assessment procedures for the Commission. After incorporating their comments, we provided a draft of this report to the Secretaries of Health and Human Services, Labor, and Transportation; and the Administrator of the Environmental Protection Agency for their review and comment.

Organization of Appendices on Chemical Risk Assessment at Selected Federal Agencies

In the following appendices, we provide more detailed information regarding the framework and methods applicable to chemical risk assessment activities of EPA, FDA, OSHA, and RSPA. There is a separate technical appendix covering each of these four agencies, along with their relevant offices, programs, or centers that are involved in conducting chemical risk assessments.

For consistency and ease of presentation, we have generally organized the appendices on each agency according to a standard format with four major sections.

1. We describe the general context for the chemical risk assessment activities of each agency. This includes a summary of the primary risk statutes, mandates, and tasks related to potential risks from exposure to chemical agents.

2. We identify and summarize the standard risk assessment procedures of each agency and, if applicable, each agency's various offices, programs, or centers. This section is generally organized by the major analytical steps of the risk assessment process: hazard identification, dose-response assessment, and exposure assessment. These correspond to the first three steps of the four-step paradigm for risk assessment as defined by NAS and used by three of the four agencies covered by our review. (We address the fourth step of the process, risk characterization, as a separate objective in the final section of each agency appendix.) Within the descriptions of those steps, we often distinguish between the procedures used for assessing cancer and noncancer effects. Given developments in risk assessment methods, these distinctions are sometimes more artificial than real.[3]

3. We present additional information about major assumptions and methodological choices in the agencies' standard risk assessment procedures. For EPA, FDA, and OSHA, the primary focus of this section is a detailed table identifying some of the major agencywide or program-specific assumptions that may be used in chemical risk assessments. To the extent that such information was available, each

[3] For example, agencies may omit or combine some of the steps in certain situations. Also, with increasing research attention on the modes of action of chemical agents, the line between procedures for identifying carcinogenic and noncancer effects is blurring.

of these tables also includes information on the agency's reason(s) for selecting a particular assumption, when in the risk assessment process the agency would apply the assumption, and the likely effect of using the assumption on risk assessment results. (Because agencies very rarely made direct comparisons of their choices to those of other agencies in their risk assessment guidelines or related documents, we have not included a separate column on that topic in the appendix tables. That objective is, however, addressed in the letter portion of this report.) The appendix on RSPA does not include all of these elements because of differences in its context and approach to chemical risk assessment.

4. The final section of each appendix addresses each agency's approach or policies for characterizing the results of risk assessments for agency decision makers and other interested parties. In particular, we describe the agency's policies or practices with regard to the transparency of risk assessment results, such as reporting the range and distribution of risks and identifying the uncertainties in the risk analysis and underlying data.

To avoid repetition in the appendices on agencies' risk assessment procedures, our most detailed descriptions of basic methods and issues appear in the EPA appendix under the discussion of agencywide procedures. Descriptions of procedures used by other agencies or programs, including the individual program offices within EPA, then reference the EPA-wide descriptions of those particular methods, if they are similar.

Although we provide much more detailed technical information in these appendices than in the main body of the report, it is still important to recognize that agencies' risk assessment methods are more involved and complex than we have described in this report. In particular, the tables of assumptions do not represent a comprehensive listing of all assumptions and choices of the agencies. Agencies might use many different types and numbers of assumptions in any given assessment, and the assumptions are being altered over time to reflect scientific improvements and changes in risk approaches and the regulatory context. However, the information presented is intended to illustrate the types and diversity of procedures and assumptions employed by the agencies we examined.

Chemical Risk Assessment at the Environmental Protection Agency

Chemical risk assessment at the Environmental Protection Agency (EPA) is a complex and diverse undertaking. The variety and range of the relevant regulatory authorities and activities has a major effect on the organization and conduct of risk assessment at the agency. An expanding set of agency guidelines reflects the evolving nature of EPA's risk assessment procedures. EPA generally follows the four-step risk assessment process identified by the National Academy of Sciences (NAS). Changes are occurring in EPA's approaches to cancer, noncancer, and exposure assessments, with a general trend toward the development and application of more complex and comprehensive methodologies. To a greater extent than the other agencies we reviewed, EPA has established a set of default assumptions (often precautionary in nature) and standard data factors for use by its risk assessors. In the "tiered" risk assessment approaches commonly employed by EPA's program offices, precautionary default assumptions are most often used during initial screening assessments, when the primary task generally is to determine whether a risk might exist and more rigorous analysis is needed. However, the information necessary for more detailed analysis is not always available, so for regulatory purposes the agency may be limited to using results from its initial tiers of risk assessments. In presenting the results of its risk assessments, it is EPA's policy that risk characterizations should be prepared in a manner that is clear, transparent, reasonable, and consistent with other risk characterizations of similar scope prepared across the programs in the agency.

The following sections describe for EPA and its component offices, the context for chemical risk assessment, the general procedures for conducting risk assessments, major assumptions and methodological choices in those procedures, and the agency's policy for risk characterization. Because chemical risk assessment at EPA is such a complex and diverse activity, this appendix can only summarize and illustrate the range of contexts, procedures, assumptions and methods, and policies that affect the conduct of EPA risk assessments. For example, as in our report as a whole, this appendix focuses primarily on human health and safety risk assessment and less on ecological risk assessment. However, we have included a brief section on EPA's ecological risk assessment guidelines under our discussion of agencywide risk assessment procedures and illustrated the role played by ecological risk assessment in the risk assessment activities of some, but not all, of EPA's program offices under our discussion of program-specific procedures. As a practical matter, this appendix reflects risk assessment topics that were addressed in agencywide or program-specific guidelines or descriptions of chemical

risk assessment at EPA. To the extent that such activities were not explicitly addressed in the agency's risk assessment guidelines and related documents, there may be little information on them in this appendix.

Context for EPA Chemical Risk Assessment

EPA is responsible for a wide range of regulatory—and related risk assessment—activities pertaining to potential health, safety, and environmental risks associated with chemical agents. This range of activities reflects an equally broad and diverse range of underlying environmental statutes. According to EPA, close to 30 provisions within the major environmental statutes require decisions based on risk, hazard, or exposure assessment, with varying requirements regarding the scope and depth of the agency's analyses. In general, EPA's regulatory authority regarding chemical agents is compartmentalized according to the various kinds and sources of exposure—such as pesticides, drinking water systems, or air-borne pollutants—and reflected in the agency's organization into various program offices—such as the Office of Air and Radiation, Office of Solid Waste, and Office of Water. Table 2 summarizes the principal statutes, regulatory tasks, and risk mandates associated with chemical risk assessment activities of EPA's offices.

Table 2: Chemical Risk Statutes, Tasks, and Mandates for EPA Offices

Office or program	Major risk-related statute(s)	Primary risk-related tasks	Primary risk-related mandate(s)
Chemical Emergency Preparedness and Prevention Office (CEPPO)	Emergency Planning and Community Right-to-Know Act (EPCRA) in the Superfund Amendments and Reauthorization Act of 1986 (SARA), Title III Clean Air Act Amendments of 1990 (CAAA)	Under EPCRA, evaluates substances for toxicity, reactivity, volatility, dispersability, combustibility, or flammability to develop and maintain a list of extremely hazardous substances and threshold quantities. Also develops regulatory requirements for reporting accidental releases and for emergency planning. Under Section 112(r) of the amended Clean Air Act (CAA), evaluates substances for acute adverse health effects, likelihood of accidental release, and magnitude of exposure to develop a list of substances for prevention of accidental release. Evaluates accidental chemical release risk management and prevention practices for development of accident-prevention and risk-reduction regulations at industrial facilities. Also under the CAAA, investigates chemical incidents, evaluates the risks associated with accidental releases, and conducts research on risk analysis and assessment.	Under EPCRA, the EPA list of extremely hazardous substances and their thresholds, along with reporting requirements, are used by state and local entities to manage the risks associated with chemical emergencies at the local level. Under Section 112(r) of the amended CAA, EPA must develop a list of at least 100 substances that pose the greatest risk of causing death, injury, or serious adverse effects to human health or the environment from accidental releases. EPA must also develop regulations for preparation and submission of risk management programs and plans by industrial facilities handling these listed substances. Also under the amended CAA, for clean air research, EPA shall develop methods and techniques necessary to identify and assess the risks to human health from accidental exposures.

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Office or program	Major risk-related statute(s)	Primary risk-related tasks	Primary risk-related mandate(s)
Office of Air and Radiation (OAR –air quality side)	Clean Air Act; Clean Air Act Amendments of 1990	Regulation of emissions of air-borne pollutants, including • setting national ambient air quality standards (NAAQS) for six "criteria" pollutants, and • setting standards for regulating emissions of hazardous air pollutants (toxic chemicals other than the criteria pollutants). Under the CAA, EPA is also required to review the scientific data upon which air quality standards are based and revise the standards, if necessary, every 5 years.	For criteria air pollutants, set standards to protect public health with an adequate margin of safety. For hazardous air pollutants, set standards using maximum achievable control technology (MACT) for a specified list of chemicals identified in the CAAA. However, if applying the MACT is found to lower risks insufficiently, EPA may pursue further regulation to control the residual risk, applying the pre-CAAA standard of providing an ample margin of safety.
Office of Emergency and Remedial Response (OERR –Superfund)	Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA); Superfund Amendments and Reauthorization Act of 1986	Remediation of hazardous waste sites, including • defining hazardous substances and the amounts of release that must be reported to EPA, • screening and ranking risks posed by hazardous waste sites and identifying action priorities among them, • evaluating need for action at hazardous waste sites, and • evaluating effectiveness of options for remediation.	Remedial actions are authorized at a site whenever any hazardous substance is released or there is a substantial threat of such a release into the environment, or when there is a release or substantial threat of release into the environment of any pollutant or contaminant which may present an imminent and substantial danger to the public health or welfare. Remedial action priorities are to be based on relative risk or danger to public health or welfare or the environment, taking into account the population at risk, the hazard potential of the hazardous substances, and the potential for contamination of air and drinking water, among other factors. Need for action is determined by evaluation of risks to human health and the environment; effectiveness is determined by meeting requirements of other laws or risk-based goals.

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Office or program	Major risk-related statute(s)	Primary risk-related tasks	Primary risk-related mandate(s)
Office of Pesticide Programs (OPP)	Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); Federal Food, Drug, and Cosmetic Act (FFDCA); Food Quality Protection Act (FQPA)	Regulation of pesticides, including • approving the registration of pesticides to set allowable uses in agriculture and extermination, and • setting tolerances for pesticide residues permitted to remain in or on foods available to the consumer.	For pesticide residues in all foods, determine whether there is reasonable certainty of no harm, with consideration of • an additional safety factor to protect infants and children, • aggregate exposure to a pesticide (including all exposures for which there is reliable information), and • cumulative exposures to pesticides with a common mechanism of toxicity. For other exposures, determine whether use of the pesticide would present any unreasonable risk to man or the environment.
Office of Pollution Prevention and Toxics (OPPT)	Toxic Substances Control Act (TSCA)	Evaluation and regulation of existing and new chemicals used in manufacturing and commerce to identify any potentially dangerous products or uses.	For chemicals listed on the inventory of "existing chemicals," determine whether use of that chemical will present an unreasonable risk to human health or the environment. For newly introduced chemicals, or significant new uses of existing chemicals, determine whether use may present an unreasonable risk to human health or the environment.

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Office or program	Major risk-related statute(s)	Primary risk-related tasks	Primary risk-related mandate(s)
Office of Solid Waste (OSW)	Resource Conservation and Recovery Act of 1976 (RCRA)	"Cradle-to-grave" regulation of hazardous waste management, including the use of risk assessment information in • defining (and delisting) substances as hazardous wastes, • evaluating the hazards posed by waste streams, • assessing the need for corrective action at disposal sites, and • granting waste disposal permits.	Hazardous waste is defined as a solid waste, or combination of solid wastes, which because of its quantity, concentration, or physical, chemical, or infectious characteristics may • cause, or significantly contribute to, an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness; or • pose a substantial present or potential hazard to human health or the environment when improperly treated, stored, transported, or disposed of, or otherwise managed. Treatment, storage, or disposal of waste is to be conducted so as to minimize the present and future threat to human health and the environment.

(Continued From Previous Page)

Office or program	Major risk-related statute(s)	Primary risk-related tasks	Primary risk-related mandate(s)
Office of Water (OW)	Clean Water Act (CWA); Safe Drinking Water Act (SDWA); SDWA Amendments of 1996	Evaluation and regulation of ambient water and drinking water quality, including • recommending water quality criteria and establishing national minimum effluent standards, • prohibiting discharge of toxic pollutants in toxic amounts, • establishing national drinking water standards for public water systems, and • identifying subpopulations at elevated risk of health effects from exposure to contaminants in drinking water and conducting studies characterizing health risk to sensitive populations from contaminants in drinking water.	Under CWA, EPA is to establish criteria for ambient water quality on the basis of health and ecological effects and accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare. Also under CWA, effluent standards for toxic pollutants are to be at that level which the EPA Administrator determines will provide an ample margin of safety, so standards more stringent than those based on the best available technology economically achievable (the normal basis) may be named at EPA discretion. Under SDWA, the EPA Administrator is to promulgate national primary drinking water regulations for each contaminant which may have any adverse effect on the health of persons and which is known or anticipated to occur in public water systems. Such regulations specify two levels of contamination • a maximum contaminant level goal (MCLG) set solely on health grounds at a level at which no known or anticipated effects on the health of persons occur and which allows an adequate margin of safety, and • a maximum contaminant level (MCL) set as close as feasible to the MCLG. The 1996 amendments to SDWA require EPA, when developing drinking water regulations, to (1) use the best available, peer-reviewed science and supporting studies and data; and (2) make publicly available a risk assessment document that discusses estimated risks, uncertainties, and studies used in the assessment.

(Continued From Previous Page)

Office or program	Major risk-related statute(s)	Primary risk-related tasks	Primary risk-related mandate(s)
Office of Research and Development (ORD)	(Not applicable; supports the efforts of other EPA program offices.)	No direct regulatory authority, but supports risk-related activities of other EPA offices by: • conducting the hazard identification and dose-response assessment steps of risk assessments for specific chemicals at the request of program offices, • preparing or assisting in the development of EPA risk assessment guidelines and policies, and • conducting complex, precedent-setting risk assessments.	(Not applicable; supports the efforts of other EPA program offices.)

Source: EPA documents and comments provided by EPA officials.

A number of other contextual factors affect the extent of involvement by EPA offices in assessing and using risk assessment information in support of the various statutes, mandates, and tasks identified in table 2.

- Risk assessment information may not be the only, or even the primary, basis for the ultimate risk management decision. EPA statutes vary fundamentally by whether the basis for regulation is (1) risk (health and environmental) only, (2) technology-based, or (3) risk balancing (consideration of risks, costs, and benefits).
- For some chemical risk assessment activities, EPA has a secondary role. Instead, the main responsibility for determining the relative risk of a chemical, compiling and analyzing risk-related data, or completing other tasks associated with a particular statute might lie with industry, states, or local entities.
- In practical terms, the resources available for conducting a risk assessment for a given chemical might limit the depth and scope of EPA's (or other parties') analysis. Such resource limitations might include not only schedule and staffing constraints, but often the amount and quality of directly relevant scientific data available for analysis.

Risk assessment activities involve both EPA's program offices and its Office of Research and Development (ORD), which is the principal scientific and research arm of the agency. ORD often does risk assessment work for EPA program offices that focuses on the first two steps in the four-step NAS process—hazard identification and dose-response assessment—in particular, the development of "risk per unit exposed" numbers. The exposure assessment and risk characterization steps tend to be the responsibility of the various regulatory programs at EPA. However, according to agency officials, both program offices and ORD may conduct all of the risk assessment steps in particular cases. For example, OW's Office of Science and Technology does all of the assessments for purposes of the SDWA, and, because of their particular statutory mandates, OPP and OPPT have developed the capability to conduct all steps of a risk assessment on their own.[1] ORD carries out all steps of highly complex, precedent-setting risk assessments of specific chemicals, such as dioxin and mercury.

[1] Also, some of the material submitted by industry petitioners seeking regulatory approvals of chemicals is confidential business information, which precludes OPP and OPPT from sharing all of their risk assessment data with other parts of EPA.

ORD also helps to coordinate the development of EPA's risk assessment methods, tools, models, and policies. In particular, much of EPA's agencywide guidance on conducting risk assessments is developed and disseminated through ORD, with input from EPA's program offices, Science Policy Council, and Science Advisory Board, as well as other external parties. Coordination of risk assessment activities also occurs through EPA's Risk Assessment Forum and the agency workgroups that approve information for entry into EPA's Integrated Risk Information System (IRIS). The Risk Assessment Forum is a standing committee of senior EPA scientists that was established to promote agencywide consensus on difficult and controversial risk assessment issues and to ensure that this consensus is incorporated into appropriate EPA risk assessment guidance. Managed by ORD, IRIS is a computerized database that contains information on human health effects that may result from exposure to various chemicals in the environment. IRIS was initially developed for EPA staff in response to a growing demand for consistent information on chemical substances for use in risk assessments, decision making, and regulatory activities. The entries in IRIS on individual chemicals represent a consensus opinion of EPA health scientists representing the program offices and ORD and have been subject to EPA's peer review policy since its issuance in 1994.[2]

Risk Assessment Procedures

There are agencywide risk assessment procedures that EPA's various program offices generally follow, but each office also has different statutory mandates and risk assessment tasks associated with its regulatory authority. These contextual differences contribute to some program-specific variations in the conduct of chemical risk assessments. In addition, EPA's procedures are in transition from more simplistic traditional methods for identifying and assessing risks to increasingly complex models and methods. It is particularly important to recognize that, while most EPA guidelines (and this appendix) distinguish between cancer and noncancer procedures, this distinction is becoming increasingly blurred as new scientific methods are being developed and applied. In general, EPA follows the NAS four-step process for human health risk assessments: (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization. However, for ecological risk assessment, EPA's guidelines recommend a three-step

[2] IRIS does not, however, incorporate OPP or OPPT risk assessment data from confidential business data.

process: (1) problem formulation, (2) analysis, and (3) risk characterization.

Guidelines

To a much greater extent than the other agencies we reviewed, EPA has documented its risk assessment procedures and policies in a voluminous and expanding set of guidelines, policy papers, and memoranda. These documents are primarily intended as internal guidance for use by risk assessors in EPA and those consultants, contractors, or other persons who perform work under EPA contract or sponsorship.[3] However, the documents also make information on the principles, concepts, and methods used in EPA's risk assessments available to other interested parties. EPA's guidelines undergo internal and external peer review.

Beginning in 1986, EPA published a series of risk assessment guidelines to set forth principles and procedures to guide EPA scientists in the conduct of agency risk assessments, and to inform agency decision makers and the public about these procedures. In general, EPA adopted the guiding principles of fundamental risk assessment works, such as the 1983 Red Book by the NAS' National Research Council (NRC).[4] EPA's guidelines supplement these principles. Five sets of guidelines were finalized in 1986, including guidelines for carcinogen risk assessment, mutagenicity risk assessment, health risk assessment of chemical mixtures, health assessment of suspect developmental toxicants, and estimating exposures.[5] In part to respond to advances and changes in risk assessment methods—but also in response to criticisms of its guidelines by NRC, among others—EPA has revised most of these guidelines, in either proposed or final form, and produced additional guidance documents.

[3] Guidelines are not rules, are not binding on either EPA or any outside parties, and do not alter applicable EPA statutes and regulations.

[4] NRC is the principal operating agency and research arm of NAS in advising and providing services to the federal government, the public, and the scientific community.

[5] Mutagenicity risk assessment focuses on analysis of agents that may cause genetic mutations. Developmental toxicity risk assessment focuses on risk to human development, growth, survival, and function because of exposure to environmental agents prior to conception, prenatally, or to infants and children.

Statutory changes have also prompted revisions and expansions of EPA's risk assessment guidelines and policy papers. In the Clean Air Act Amendments of 1990, for example, Congress directed EPA to revise its carcinogen risk assessment guidelines, taking into consideration the NAS recommendations, before making any determinations of the "residual risks" associated with emissions of hazardous air pollutants.[6] The results of the NAS study appeared in the 1994 NRC report, *Science and Judgment in Risk Assessment*. Among other things, NRC recommended that EPA better identify the inference (default) assumptions in its guidelines, explain the scientific or policy bases for selecting them, and provide guidance on when it would be appropriate to depart from the assumptions.

The current set of agencywide risk assessment guidelines and policies includes the following major topics:[7]

- carcinogen risk assessment,
- neurotoxicity risk assessment,
- reproductive toxicity risk assessment,
- developmental toxicity risk assessment,
- mutagenicity risk assessment,
- health risk assessment of chemical mixtures,
- guidelines for exposure assessment,
- guidelines for ecological risk assessment,
- other risk assessment tools and policies,
  - probabilistic analysis in risk assessment,
  - use of the benchmark dose approach in health risk assessment,
  - reference dose (RfD) and reference concentration (RfC),
  - evaluating risk to children, and
  - EPA risk characterization program.

In addition to these agencywide documents, there are also numerous program-specific guidelines and policy documents. For example, the *Risk Assessment Guidance for Superfund* series covers various stages of human health evaluation as well as ecological risk assessment and probabilistic risk assessment. There are also guidelines and policy memoranda at the headquarters and regional office level that supplement

[6] Residual risks are those remaining after the maximum achievable control technology is in effect.

[7] There are other documents, but they are mostly on narrow topics—the assessment of thyroid follicular cell tumors, for example.

these general Superfund guidelines. Similarly, OPP, with input from ORD, has developed a series of science policy papers specifically on issues related to pesticide risk assessments, in response to provisions of the Food Quality Protection Act of 1996.

Describing EPA's risk assessment procedures with any certainty is a difficult task, given the sheer volume of EPA guidance documents, the continuing evolution of risk assessment practices, and the extent to which many of EPA's revisions are currently draft in nature. For example, the official guidelines for cancer risk assessment are still the 1986 version, but the agency published a proposed revision of those guidelines in 1996, and continued to revise them in 1999, but the revised guidelines have not yet been made final by EPA.[8] Although the various revisions since 1986 do not represent official agency policy at this stage, the approaches that they describe are likely to provide a more accurate reflection of current practices and directions in EPA risk assessments. To some extent EPA is already applying these newer approaches, for example in the Office of Water's revised methodology for deriving ambient water quality criteria for the protection of human health and the Office of Pesticide Programs' Cancer Peer Review Committee.

Agencywide Risk Assessment Procedures

The following sections summarize the basic elements of EPA's agencywide procedures for conducting risk assessments. Because most of EPA's guidelines focus on human health risks, this section also focuses primarily on health assessments in describing EPA's general approach. EPA generally uses the NAS four-step process for those assessments. However, a separate short section on EPA's approach to ecological risk assessment appears at the end of this agencywide summary. Also, while this appendix (and most of the source material from which it was derived) discusses procedures for assessing cancer and noncancer effects separately, this distinction is increasingly artificial. As EPA noted in its *Strategy for Research on Environmental Risks to Children*, the agency is less likely to consider cancer and noncancer endpoints in isolation as it develops and incorporates more advanced scientific methods to measure and model the biological events leading to adverse effects.[9] According to EPA, the science

[8] A particular focus of changes in the 1999 version is additional attention to issues of human variability, especially risks to children versus adults.

[9] EPA/600/R-00-068 (August 2000).

of risk assessment is moving toward a harmonization of the methodology for cancer and noncancer assessments.

Hazard Identification

Carcinogens

EPA's approach to hazard identification changed significantly between the agency's 1986 guidelines and its proposed revision. In its 1986 guidelines, EPA defined a hierarchical classification scheme for hazard identification of chemical agents (see table 3). In this scheme, analysis of whether an agent is a potential human carcinogen proceeds through distinct steps based on the type of human, animal, or "other" evidence available and its quality (whether such evidence is sufficient, limited, or inadequate), resulting in classification of the agent in one of six alphanumeric categories.

Table 3: EPA's 1986 Classification System for Characterization of Carcinogenicity

Group	Description	Weight of evidence for carcinogenicity
A	Human carcinogen	Sufficient evidence from epidemiologic (human) studies
B1	Probable human carcinogen	Limited evidence from epidemiologic studies
B2	Probable human carcinogen	Sufficient evidence from animal studies and inadequate evidence or no data from epidemiologic studies
C	Possible human carcinogen	Limited evidence in animals and absence of adequate human data
D	Not classifiable	Inadequate or no data
E	Evidence of noncarcinogenicity for humans	No evidence in adequate studies in at least two species or in both epidemiologic and animal studies

Source: Adapted from EPA's 1986 *Guidelines for Carcinogen Risk Assessment* and other agency documents that describe the agency's classification system.

In response to further developments in the understanding of carcinogenesis, and to address limitations of its 1986 scheme, EPA proposed a revised approach that melds the separate human-animal-other processes into a single comprehensive evaluation. In this approach, weighing the evidence and reaching conclusions about the carcinogenic potential of an agent would be accomplished in a single step after assessing all individual lines of evidence. Compared to the 1986 guidelines, the proposed revision also encourages fuller use of all biological information—instead of relying primarily on tumor findings—and emphasizes analysis of the agent's mode of action in leading to tumor development.[10]

EPA's proposed revision replaces the 1986 alphanumeric classifications with a "weight of evidence" narrative to provide more complete information not only on the likelihood of human carcinogenic effects but also the conditions under which such effects may be expressed. To provide some measure of consistency in the narratives, standard descriptors are to be utilized to express the conclusion regarding the weight of evidence for carcinogenic hazard potential. These descriptors have also been undergoing some changes, but, according to EPA's July 1999 discussion draft, would include:

1. carcinogenic to humans,
2. likely to be carcinogenic to humans,
3. suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential,
4. data are inadequate for an assessment of human carcinogenic potential, and
5. not likely to be carcinogenic to humans.

The narrative might also reflect more than one conclusion for a given agent. For example, a narrative could say that an agent is likely to be carcinogenic by inhalation exposure but not likely to be carcinogenic by oral exposure.

Noncancer effects

[10] "Mode of action" is defined as a series of key events and processes, starting with interaction of an agent with a cell and proceeding through operational and anatomical changes resulting in cancer formation.

EPA starts with a review and assessment of the toxicological database to identify the type and magnitude of possible adverse health effects associated with a chemical. Exposure to a given chemical might result in a variety of toxic effects, so EPA has produced separate guidelines for the assessment of mutagenicity, developmental toxicity, neurotoxicity, and reproductive toxicity.[11] However, assessments for these noncancer health effects may also overlap. For example, developmental effects might be traced to exposures and factors also covered by reproductive toxicity assessments, and developmental exposures may result in genetic damage that would require evaluation of mutagenicity risks. The EPA guidelines for noncancer effects are not step-by-step manuals, and they do not prescribe a hazard identification classification scheme. Instead, they focus on providing general advice to risk assessors on different types of toxicity tests or data and on the appropriate toxicological interpretation of test results (e.g., which outcomes should be considered adverse effects).

In addition to considering the types and severity of potential adverse effects, hazard identification would also consider and describe the nature of exposures associated with these effects. A review of the full range of possibilities would consider:

- acute effects—generally referring to effects associated with exposure to one dose or multiple doses within a short time frame (less than 24 hours, for example);
- short-term effects—associated with multiple or continuous exposure occurring within a slightly longer time frame, usually over a 14-day to 28-day time period;
- subchronic effects—associated with repeated exposure over a limited period of time, usually over 3 months; and
- chronic effects—associated with continuous or repeated exposure to a chemical over an extended period of time or a significant portion of the subject's lifetime.

Procedurally, there is an important variation from the distinct four steps of the risk assessment paradigm. In its guidelines, EPA notes that its normal practice for assessments of noncancer health effects is to do hazard

[11] Neurotoxicity focuses on adverse changes in the structure or function of the central or peripheral nervous system following exposure to a chemical, physical, or biological agent. Reproductive toxicity focuses on toxic effects on the male and female reproductive systems, including outcomes of pregnancy and lactation. Mutagenicity and developmental toxicity were described in a previous footnote.

identification in conjunction with the analysis of dose-response relationships. This is because the determination of a hazard is often dependent on whether a dose-response relationship is present. According to EPA, this approach has the advantages of (1) reflecting hazards in the context of dose, route, duration, and timing of exposure; and (2) avoiding the potential to label chemicals as toxicants on a purely qualitative basis.

Dose-Response Assessment

Carcinogens

Risk assessors conducting dose-response assessments must make basic choices regarding which data to base analyses upon and which models and assumptions to use for extrapolation of study results to the potential human exposures of regulatory interest. Data choices focus on the availability and quality of human or animal studies. Three of the more important extrapolation tasks are estimation of low-dose relationships (i.e., those that fall below the range of observation in the studies supporting the agency's analysis), calculation of toxicologically equivalent doses when dose-response data from animal studies are applied to human exposures, and extrapolating results from data on one route of exposure to another route.[12]

- Data choices

The two main types of studies that provide data useful in a quantitative dose-response assessment are (1) epidemiological studies of human populations and (2) toxicological laboratory studies using animals or, sometimes, human cells. Epidemiological studies examine the occurrence of adverse health effects in human populations and attempt to identify the causes. At a minimum, such studies can establish a potential link between exposures to chemical agents and the occurrence of particular adverse effects by comparing differences in exposed and nonexposed populations. If there is adequate information on the exposure levels associated with adverse effects, these studies can also provide the basis for a dose-response assessment. Because such data obviate the need to extrapolate from animals to humans, EPA (like other agencies) prefers to use data from epidemiological studies, if available.

[12]Risk assessors might also need to make other types of extrapolations (e.g., when estimating effects for less than a full lifetime).

Often, however, the available data for dose-response assessment will come from animal studies. A common assumption underlying risk assessments by EPA (and other agencies) is that an agent that produces adverse effects in animals will pose a potential hazard to humans. EPA's guidelines emphasize that case-specific judgments are necessary in considering the relevance of particular studies and their data. However, in the absence of definitive information to the contrary, EPA's guidelines establish some standard default choices to assist risk assessors in selecting which studies and data to use. (See the section on assumptions in this appendix for more information on such default choices and assumptions.)

- Extrapolation to low doses

Quantifying risks engenders another set of issues and choices. In particular, some type of low-dose extrapolation is usually necessary, given that the doses observed in studies tend to be higher than the levels of exposure of regulatory concern. There are limits to the ability of both epidemiological and toxicological studies to detect changes in the likelihood of health effects with acceptable statistical precision, especially at the low-dose exposures typical of most environmental exposures and given practical limits to the sizes of research studies.

A number of different models might be used for extrapolation, all giving plausible results. In its proposed revision of the carcinogen risk assessment guidelines, EPA identifies use of a biological extrapolation model as the preferred approach for quantifying risk. Such models integrate events in the carcinogenic process throughout the dose-response range from high to low doses and include physiologically based pharmacokinetic (PBPK) and biologically based dose-response models. PBPK models address the exposure-dose relationship in an organism taken as a whole, estimating the dose to a target tissue or organ by taking into account rates of absorption into the body, metabolism, distribution among target organs and tissues, storage, and elimination of an agent. Biologically based dose-response models describe specific biological processes at the cellular and molecular levels that link target-organ dose to the adverse event. These models are useful in extrapolation between animals and humans and between children and adults because they allow consideration of species- and age-specific data on physiological factors affecting dose levels and responses. However, biological models require substantial quantitative data and adequate understanding of the carcinogenic process for a specific agent. EPA cautions that the necessary data for using such

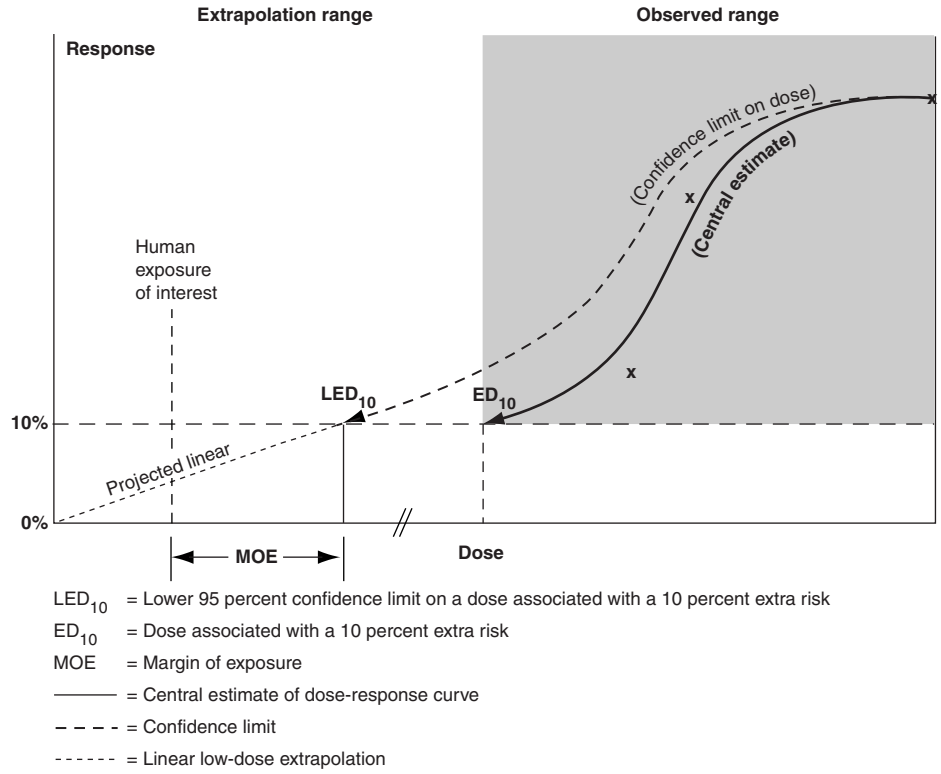
models will not be available for most chemicals. Therefore, the agency's guidelines describe alternative methods.

Dose-response assessment is a two-step process when a biologically based model is not used. The first step is the assessment of observed data to derive a point of departure, and the second step is extrapolation from that point of departure to lower (unobserved) exposures. According to EPA guidelines, the agency's standard point of departure for animal studies is the effective dose (ED) corresponding to the lower 95-percent confidence limit on a dose associated with 10-percent extra risk (LED_{10}) compared to the control group.[13] EPA may use a lower point of departure for data from human studies of a large population or from animal studies when such data are available. For the extrapolation step, EPA's proposed guidelines provide three default approaches which assume, respectively, that the dose-response relationship is linear, nonlinear, or both. The choice of which default approach to apply is to be based on the available information on the mode(s) of action of the chemical agent.

In the absence of sufficient mode of action information, or if the available mode of action information indicates that the dose-response curve at low doses is expected to be linear, the default is to use a linear approach for the extrapolation step. The assumption of linearity is generally considered a conservative, public-health protective default, intended to avoid underestimating risks at low doses. It is rooted in EPA's traditional assumption for suspected carcinogens that no threshold exists regarding adverse effects (i.e., any exposure to carcinogenic substances, no matter how small, poses some risk of developing cancer). A linear, no-threshold model generally assumes that adverse health effects are proportional to exposure for any dose above zero. The linear approach is to draw a straight line between the point of departure from observed data—typically the LED_{10}—and the origin (zero incremental dose, zero incremental response). (See fig. 3 below.) According to EPA's guidance, this linear default approach is thought to generally provide an upper-bound calculation of potential risk at low doses. The agency also pointed out that it gives numerical results about the same as a linearized multistage approach, which is the default approach under the 1986 cancer guidelines.

[13] According to EPA, the LED_{10} is chosen to account protectively for experimental variability and is an appropriate representative of the lower end of the observed range, because the limit of detection in studies of tumor effects is about 10 percent.

Figure 3: Extrapolation for Carcinogens



Source: EPA *Proposed Guidelines for Carcinogen Risk Assessment.*

The default changes to a "margin of exposure" analysis when (1) adequate data on mode of action show that linearity is not plausible, and (2) the data provide sufficient evidence to support a nonlinear mode of action for the general population and any sub-populations of concern. Rather than estimating the probability of effects at low doses, a margin of exposure analysis compares the point of departure from study data with the dose associated with the environmental exposure(s) of interest by computing the ratio between the two. (See fig. 3 for a graphical representation of these two points.) If the available evidence indicates that the dose-response may be adequately described by both a linear and a nonlinear approach, EPA's default is to present both the linear and the margin of exposure analysis.

- Extrapolation from animal to human-equivalent doses

When dose-response relationships are being extrapolated from the observed results of animal studies, it is also necessary to estimate what doses are of equivalent risk in the experimental animals (usually mice or rats) and humans. The objective of this interspecies "scaling" is to define dose units that are presumed to lead to equivalent risk across species. Not only are rodents much smaller in size than humans, but they have shorter life spans and quicker metabolisms, all of which affect the equivalent dose. For carcinogens, EPA's historical default had been to assume that end-of-life cancer risks will be equivalent across species when lifetime dosing is proportional to each species' body surface area. In practice, this "surface area scaling" was calculated by using daily milligrams scaled by the 2/3-power of the species' body weight. EPA's draft revision of the carcinogen guidelines presents a default for oral dose of scaling daily applied doses in proportion to body weight raised to the 3/4- power. This would be consistent with the 1992 recommendation from an interagency group.[14] Scaling by this method generally results in human risk estimates that are slightly lower than those obtained from surface area scaling.

For cross-species scaling of inhalation exposures, EPA uses a different approach—its reference concentration (RfC) methodology—to determine what is toxicologically equivalent. In the RfC approach, the agency estimates the respiratory deposition of particles and gases and the internal doses of gases with different absorption characteristics. EPA uses this approach because it is the concentration needed to produce an equivalent rate of loading the target tissue with deposited or absorbed chemical agent that is important in inhalation exposures, not simply the dose in the air.

[14] FDA and OSHA traditionally used an alternative assumption that risks are equivalent when dosing is proportional to each species' body weight but are now also using or considering $(\text{body weight})^{3/4}$.

- Extrapolation to different routes of exposure

Exposure to a chemical agent may occur through inhalation, oral ingestion, or dermal contact. However, the data being used for a risk assessment may only reflect one of these routes of exposure, and that route may be different than the route of concern to agency regulators in a particular case. For example, available animal study data might indicate that ingestion of a chemical substance is associated with cancer, but risk assessors may need to consider the relevance of this ingestion data to the prediction of risks associated with inhalation exposures. In general, it is EPA's position that adverse effects manifested through one route of exposure are relevant to consideration of any other route of exposure. However, EPA's guidelines also caution that such route-to-route extrapolation should be consistent with existing biological information.[15]

Noncancer effects

In contrast to its assessments of cancer risks, EPA's traditional view of noncancer toxic effects has been that a threshold exists. In other words, the agency typically assumes that noncancer adverse effects occur only after a threshold level of exposure to an agent has been exceeded.[16] For noncancer effects, the primary objective of the agency's assessment is to derive an RfD or, in the case of inhalation exposures, an RfC representing a concentration of the agent in the air rather than a dose. This RfD or RfC is an estimate of a daily exposure to an agent by the human population (including sensitive sub-groups) that is expected to be without an appreciable risk of deleterious effects during a lifetime. For most of its history, EPA has relied on a no observed adverse effect level (NOAEL) approach to estimate the RfD. However, the agency may also use other approaches, such as the benchmark dose approach, depending on the quality and type of data available. The NOAEL and benchmark dose approaches are described in more detail below.

[15] For example, a chemical that acts as a carcinogen because of the way the body metabolizes it via one route—such as ingestion into the stomach transforming the chemical into a toxin—may not be metabolized in the same way by another route. Carcinogenic effects, therefore, would not be expected via another route of exposure that does not produce this same metabolite.

[16] There are, however, exceptions to this general rule, such as reproductive toxicants that may act through genetic mutation mechanisms. In such cases, EPA will use the no-threshold approach described for suspected carcinogens.

Similar to other agencies, EPA's traditional procedure for addressing noncancer effects has been to define a NOAEL from experimental data and then apply uncertainty factors to estimate an RfD or RfC. In this approach, toxicologists first seek to identify the top of the range of dose levels without any observed adverse effect in animals.[17] Then, to estimate a dose to humans that will be similarly without effect, this dose level is divided by a set of uncertainty factors, typically factors of 10.[18] These uncertainty factors are used to account for the possibility of greater sensitivity among humans than in experimental animals, of greater sensitivity in some humans compared to average humans, and for other concerns. One such concern is if there was no dose in a study at which harmful effects were not detected. In such cases, extrapolation is instead based on the lowest observed adverse effect level (LOAEL), but an additional uncertainty factor would then be incorporated in the agency's estimated dose. The choice and size of factors (e.g., 10 or 3) can vary from case to case, and EPA's guidelines note that professional scientific judgment must be used in assigning uncertainty and modifying factors. EPA typically uses two or three factors (a division of the NOAEL dose by 100- to 1000-fold), and, under current policy, generally will use a maximum uncertainty factor of no greater than 3,000.[19] However, EPA may also reduce the standard uncertainty factors if it has more informative pharmacokinetic data about variability among humans or across species. An additional "modifying" factor may also be used when the areas of scientific uncertainty addressed with uncertainty factors do not represent all of the uncertainties in the estimation of a reference dose or concentration.

EPA may also use the benchmark dose approach to identify a dose without appreciable effect from an experimental study. Unlike the NOAEL approach, the benchmark dose approach uses the entire set of available data on doses and responses; it is not limited to only considering the specific dose levels tested in the study. In this benchmark dose approach,

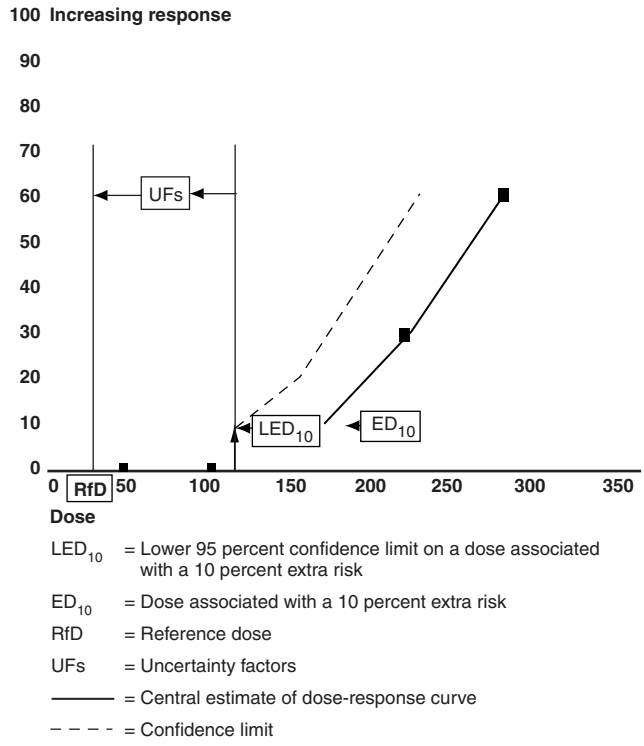
[17] Sometimes, a no observed effect level (NOEL) is used instead of a NOAEL.

[18] These are often referred to as "safety factors" by other agencies and in general risk assessment literature. EPA, however, uses the term uncertainty factor instead of safety factor because of concerns that the latter implies an absolutely safe level, an assurance that the agency does not believe it can provide.

[19] It is EPA's opinion that toxicity databases that are weaker and would result in uncertainty factors in excess of 3,000 are too uncertain as a basis for quantification. In such cases, EPA no longer estimates an RfD. Before this policy was in place, factors of 10,000 were applied for a few chemicals.

researchers fit a dose-response curve using all of the data in the observed experimental range. EPA would typically use the modeled LED_{10} dose as a point of departure to derive an RfD, and the agency would still apply uncertainty factors to this dose, as in the NOAEL approach. (See fig. 4.)

Figure 4: Derivation of a Reference Dose Using the Benchmark Dose Approach



Source: EPA *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000); Technical Support Document Volume 1: Risk Assessment*.

Exposure Assessment

EPA's program offices usually perform the exposure assessment step, given the different exposure scenarios of interest for the separate regulatory programs.[20] However, EPA has published agencywide guidelines for exposure assessment that describe general principles and practices for conducting such assessments. The focus of EPA's guidelines is on human exposures to chemical substances, but the agency noted that much of the guidance also applies to wildlife exposure to chemicals or human exposure to biological, physical (e.g., noise), or radiological agents.[21] EPA points out, though, that assessments in these other areas must consider additional factors that are beyond the scope of the exposure assessment guidelines.

EPA's guidelines establish a broad framework for agency exposure assessments by describing the general concepts of exposure assessment, standardizing the terminology (such as defining concepts of exposure, intake, uptake, and dose), and providing guidance on the planning and implementation of an exposure assessment. The guidelines are not, however, intended to serve as a detailed instructional guide. EPA's guidance prescribes no standard format for presenting exposure assessment results, but recommends that all exposure assessments, at a minimum, contain a narrative exposure characterization section that

- provides a statement of purpose, scope, level of detail, and approach used in the assessment, including key assumptions;
- 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;
- 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; [22]
- interprets the data and results; and

[20] As mentioned earlier in this appendix, sometimes ORD may do the entire risk assessment, including the exposure assessment step.

[21] The guidelines also discuss the implications for exposure assessment if the assessment is to be used for purposes other than risk assessment (e.g., to determine whether exposure occurs, to monitor status and trends, or to establish exposure-incidence in epidemiologic studies).

[22] The guidelines note that it is common for the single largest source of uncertainty in an exposure assessment to be the estimate of the duration of an individual's contact with a chemical at a given concentration. The concentration of the chemical in the media (e.g., air, soil, or water) often is known with more certainty than the activities of the exposed individual(s).

- communicates the results of the exposure assessment to the risk assessor, who can then use this information with the results from other risk assessment elements to develop the overall risk characterization.

The guidelines encourage agency staff to use multiple "descriptors" of both individual and population risks, rather than a single descriptor or risk value. The exposure guidelines also emphasize the use of more realistic estimates of high-end exposures than had been the case in some previous practices. In the past, EPA sometimes relied on exposure estimates derived from a hypothetical "maximally exposed individual" who might spend, for example, a 70-year lifetime drinking only groundwater with the highest concentrations of contaminants detected. According to the 1997 report of the Presidential/Congressional Commission, this approach was often based on such unrealistic assumptions that it impaired the scientific credibility of risk assessments. Now, however, EPA has adopted the use of distributions of individual exposures as the preferred practice. EPA's guidance indicates that risk assessments should include both central estimates of exposure (based on either the mean or median exposure) and estimates of the exposures that are expected to occur in small, but definable, high-end segments of the population. EPA states that a high-end exposure estimate is to be a plausible estimate of the individual exposure for those persons at the upper end of an exposure distribution. The agency's intent is to convey an estimate of exposure in the upper range of the distribution, but to avoid estimates that are beyond the true distribution.[23]

EPA has identified several new directions in its approach to exposure assessment. First is an increased emphasis on total (aggregate) exposure via all pathways. EPA policy directs all regulatory programs to consider in their risk assessments exposures to an agent from all sources, direct and indirect, and not just from the source that is subject to regulation by the office doing the analysis. Another area of growing attention is the consideration of cumulative risks, when individuals are exposed to many chemicals at the same time. The agency is also increasing its use of probabilistic modeling methods, such as Monte Carlo analysis, to analyze variability and uncertainty in risk assessments and provide better estimates of the range of exposure, dose, and risk in individuals in the population.

[23] The guidelines state that, conceptually, the high end of the distribution means above the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest exposure.

EPA policy directs regulatory programs to pay special attention to the risks of children and infants.

EPA has produced some reference documents for exposure assessments, such as the *Exposure Factors Handbook*.[24] This handbook is intended to provide parameter values for use across the agency and to encourage use of reasonable exposure estimates by providing appropriate data sources and suggested methods. The handbook provides a summary of available statistical data on various factors used to assess human exposure to toxic chemicals. These factors include: drinking water consumption; soil ingestion; inhalation rates; dermal factors including skin area and soil adherence factors; consumption/intake of fruits and vegetables, fish, meats, dairy products, homegrown foods, and breast milk; human activity patterns, such as time spent performing household tasks; consumer product use; and residential characteristics. EPA provides recommended values for the general population and also for various segments of the population who may have characteristics different from the general population (e.g., by age, gender, race, or geographic location). EPA guidance cautions, though, that these general default values should not be used in the place of known, valid data that are more relevant to the assessment being done. The default values used in EPA risk assessments, however, sometimes vary slightly from the recommended values appearing in the handbook. For example, while the handbook's mean recommended value for adult body weight is 71.8 kilograms (kg), the handbook also noted that a value of 70 kg has been commonly assumed in EPA's risk assessments. Similarly, the recommended value to reflect average life expectancy of the general population is 75 years, but 70 years also has been commonly assumed in EPA risk assessments. Officials from EPA program offices pointed out that they may use different exposure factors in their risk assessments because they sometimes develop exposure assessment methods specific to their programs using different data sources or population characteristics than those used by ORD for the *Exposure Factors Handbook*.

Ecological Risk Assessment

Ecological risk assessment is different from human health risk assessment in that it may examine entire populations of species and measure effects on partial or whole ecosystems. Often, the focus is on not just a single ecological entity, but on the potential adverse effects on multiple species

[24] The agency also has a *Wildlife Exposure Factors Handbook* for ecological risk assessments, and a *Children's Exposure Factors Handbook* is also in development.

and their interactions (for example, on the food chain). While human health risk assessment is primarily concerned with an agent's toxicity to humans, ecological risk assessment might consider a range of adverse effects on natural resources (such as crops, livestock, commercial fisheries, and forests), wildlife (including plants), aesthetic values, materials or properties, and recreational opportunities. For example, a chemical agent could be considered a risk to wildlife if exposure to it caused death, disease, behavioral abnormalities, mutations, or deformities in the members of a species or their offspring. It could be considered a risk to aesthetic values if it affected the color, taste, or odor of a water source.

By EPA's definition, ecological risk assessment is a process that evaluates the likelihood that adverse ecological effects may occur or are occurring as a result of exposure to one or more "stressors." In other words, ecological risk assessments may be prospective or retrospective, and, in many cases, both approaches are included in a single risk assessment. Chemicals are only one of the possible ecological stressors that EPA might consider, along with physical and biological ones.[25] EPA's guidance focuses on stressors and adverse ecological effects generated or influenced by human activity, which could be addressed by the agency's risk management decisions.

In comparison to human health risk assessment procedures, the approaches for ecological risk assessment are more recent and less well developed. However, as these methods have changed to incorporate and better characterize dynamic, interconnected ecological relationships, EPA has updated its guidance documents on the subject, with input from multiple interested internal and external parties. According to EPA, the solicitation of input from an array of sources is based, in part, on the need to establish a framework for characterizing risks based on numerous stressors, interconnected pathways of exposure, and multiple endpoints (adverse effects).

[25] For example, the alteration of a wildlife habitat would be a physical stressor and the introduction of a nonnative invasive species would be a biological stressor.

The most recent version of EPA's framework appears in *Guidelines for Ecological Risk Assessment*, published in 1998.[26] EPA's guidelines describe an iterative three-phase process consisting of problem formulation, analysis, and risk characterization. These guidelines incorporate many of the concepts and approaches called for in human health risk assessments. However, particularly in the addition of a problem formulation phase, the ecological risk assessment framework deviates from the standard four-step process used for human health risk assessments. EPA pointed out that, unlike human health assessments where the species of concern and the endpoints (e.g., cancer) have been predetermined, ecological risk assessments need a phase that focuses on the selection of ecological entities and endpoints that will be the subject of the assessment. Table 4 summarizes the activities and expected outcomes for each of the three phases of an ecological risk assessment. Prior to these phases, according to EPA, a planning stage occurs during which risk assessors, risk managers, and other interested parties are to have a dialogue and scope the problem.

Table 4: Summary of EPA's Ecological Risk Assessment Process

Phase	Actions	Products
Problem formulation	• Articulate purpose for assessment • Define problem • Determine plan for analyzing and characterizing risk • Integrate available information on sources, stressors, effects, and ecosystem and receptor characteristics	• Assessment endpoints • Conceptual models • Analysis plan
Analysis	• Characterize exposure • Characterize ecological effects	• Exposure profile • Stressor-response profile
Risk characterization	• Estimate risk • Summarize assumptions, scientific uncertainties, and strengths and limitations of the analyses	• Risk description

Source: EPA *Guidelines for Ecological Risk Assessment*.

Among the things considered during problem formulation is the selection of assessment endpoints, which are "explicit expressions of the actual environmental value that is to be protected." This is unlike human health

[26] EPA has published other, more detailed guidance documents addressing specific ecological risk assessment topics relevant to its program offices. For example, *Ecological Risk Assessment Guidance for Superfund: Process for Designing and Conducting Ecological Risk Assessments* from 1997 is specific to EPA's Superfund Program requirement for an ecological risk assessment.

assessments, where the species of concern and the endpoints have been predetermined. The selection of endpoints at EPA has traditionally been done internally by program offices, but more recently, affected parties or communities are assisting in the selection of endpoints with their selection based on ecological relevance, susceptibility, and relevance to management goals. Furthermore, conceptual models are developed during the problem formulation phase. Such models contain risk hypotheses in the form of written descriptions and visual representations, outlining predicted relationships between ecological entities and the stressors to which they may be exposed. According to EPA the hypotheses are in effect assumptions, being based on theory and logic, empirical data, mathematical models, probability models, and professional judgment.

Subsequently, during the analysis phase data are selected that will be used on the basis of their utility for evaluating risk hypotheses. The major items considered during this phase are the sources and distribution of stressors in the environment, the extent of contact and stressor-response relationships, the evidence for causality, and the relationship between what was measured and the assessment endpoint(s). Field studies involving statistical techniques (i.e., correlation, clustering, or factor analysis), surveys, the formation of indices, and the use of models are approaches to evaluating the determined risk hypotheses. (EPA's guidance on the risk characterization phase of an ecological risk assessment is discussed in the final section of this appendix.)

Program-Specific Risk Assessment Procedures

EPA's various program offices generally follow the agencywide risk assessment procedures and guidelines described above. The major exception to this is the Chemical Emergency Preparedness and Prevention Office, which does not follow the NAS four-step process for its risk assessment procedures because of its focus on risks associated with accidental chemical releases. Overall, there is great diversity in the context for risk assessment activities across EPA's program offices. Each program has different statutory mandates and risk assessment tasks associated with its specific regulatory authority, and these contribute to variations in the way the offices conduct risk assessments. In particular, there are differences in the exposure assessment step across, and sometimes within, EPA's program offices. This is not surprising, given that EPA's regulatory authorities regarding chemical agents primarily vary according to types and sources of exposure. Although there are overlaps in these various exposures to chemicals, EPA's program offices generally assess and regulate different aspects of the risks associated with exposures to humans

and/or the environment. There are also some variations in the conduct of hazard identification and dose-response analysis. The following sections summarize the risk assessment activities and procedures of those EPA program offices that are most likely to conduct assessments involving chemical risks. The descriptions highlight some of the major variations and similarities across the program offices.

Office of Pesticide Programs

OPP is part of EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS). The primary risk assessment-related activities of OPP are the registration of pesticides and the setting of tolerances for pesticide residues.[27] Registration involves the licensing of pesticides for sale and use in agriculture and extermination. No chemical may be sold in the United States as a pesticide without such registration, which establishes the conditions of legal use. All uses within the scope of the registration conditions and limits are permissible, although actual practice may vary. Pesticide tolerances are the concentrations (maximum pesticide residue levels) permitted to remain in or on food, as it is available to the consumer. Registrations and tolerances are obtained through petitions to OPP. The petitioner has the primary responsibility to provide the data needed to support registration and tolerances, including information on the toxicological effects of the pesticide.

There are three major risk statutes affecting EPA's actions regarding pesticides. Registration is carried out under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Tolerances are established under the Federal Food, Drug, and Cosmetic Act (FFDCA).[28] In 1996, Congress amended both FIFRA and FFDCA through the FQPA, which mandated some key changes in risk assessment of pesticides.

Major features and characteristics of chemical risk assessment by OPP are summarized below.

- OPP conducts all steps of risk assessments. Because OPP generally follows the NAS four-step process for human health risk assessment and

[27] The term "pesticide" includes many kinds of ingredients used in products, such as insecticides, fungicides, rodenticides, insect repellants, weed killers, antimicrobials, and swimming pool chemicals, which are designed to prevent, destroy, repel, or reduce pests of any sort.

[28] While EPA administers the setting of pesticide tolerances, FDA has authority over enforcement of the tolerances.

the EPA-wide risk assessment guidelines, most of its procedures mirror those used elsewhere in the agency.

- OPP officials noted that, over the last three decades, their office has developed a rigorous process to support the development of chemical risk assessments. This process includes regulations to establish baseline data requirements and published guidelines for conducting required studies. OPP officials emphasized the transparency of the process used to develop EPA's risk assessment procedures and the transparency of the procedures EPA uses to make decisions on the risk of individual pesticides. As an example, they noted that their program has consulted with outside experts and asked for public comment on its guidelines for reviewing studies, science policies for assessing the significance of study data, and standard operating procedures for implementing these policies in the development of a hazard identification or exposure assessment for a chemical. They also pointed out that OPP adopted a public participation process for reregistration and tolerance reassessment decisions on registered pesticides and that they publish for public comment proposed tolerances for proposed new uses of pesticides. In some circumstances, OPP consults with outside experts concerning a risk assessment of an individual pesticide.

- Pesticide registration decisions are based primarily on OPP's evaluation of the test data provided by petitioners (applicants). EPA has established a number of requirements, such as the Good Laboratory Practice Standards, to ensure the quality and integrity of pesticide data. OPPTS has also developed harmonized test guidelines for use in the testing of pesticides and toxic substances and the development of test data that must be submitted to EPA for review under federal regulations.[29] Depending on the type of pesticide, OPP can require more than 100 different tests to determine whether a pesticide has the potential to cause adverse effects to humans, wildlife, fish, and plants.

[29] OPPTS developed these guidelines through a process of harmonization that blended the testing guidance and requirements that existed in OPP, OPPT, and guidelines published by the Organization for Economic Cooperation and Development. The purpose of harmonizing these guidelines into a single set of OPPTS guidelines was to minimize variations among the testing procedures that must be performed to meet EPA data requirements under FIFRA (for OPP) and TSCA (for OPPT). The pesticide data requirements are set out in 40 CFR 158.

- The FQPA established a single, health-based standard—"reasonable certainty of no harm"—for pesticide residues in all foods.[30] All existing tolerances that were in effect when the FQPA was passed are to be reevaluated by 2006 to ensure that they meet the new safety standard. The law requires EPA to place the highest priority for tolerance reassessment on pesticides that appear to pose the greatest risk. To make the finding of "reasonable certainty of no harm" OPP considers:

1. the toxicity of the pesticide and its break-down products;

2. how much of the pesticide is applied and how often; and

3. how much of the pesticide remains in or on food by the time it is marketed and prepared (the residue).

- Among other key changes affecting OPP's risk assessments when setting tolerances, the FQPA requires the agency to:

1. Explicitly address risks to infants and children and to publish a specific safety finding before a tolerance can be established. It also requires an additional tenfold uncertainty factor (unless reliable data show that a different factor will be safe) to account for the possibly greater sensitivity and exposure of children to pesticides.

2. Consider aggregate exposure from a pesticide, including all anticipated dietary and all other exposures for which there is reliable information. These include exposures through food, drinking water, and nondietary exposures encountered through sources in the home, recreational areas, and schools.[31]

3. Consider cumulative exposures to pesticides with a common mechanism of toxicity, which previously had been considered separately.[32]

[30] This eliminated problems caused by prior differences in the standards that applied to raw versus processed foods.

[31] Occupational exposures are regulated separately.

[32] See *Children and Pesticides: New Approach to Considering Risk Is Partly in Place* (GAO/HEHS-00-175, Sept. 11, 2000) for more detailed information on EPA's progress in implementing the FQPA provisions.

- Title III of the FQPA also requires certain data collection activities of the Secretary of Agriculture, in consultation or cooperation with the Administrator of EPA and the Secretary of Health and Human Services, regarding food consumption patterns, pesticide residue levels, and pesticide use that, according to EPA, affect its risk assessments when setting tolerances.

- Also as a result of the FQPA, OPP uses a population adjusted dose (PAD), which involves dividing the acute or chronic reference dose by the FQPA uncertainty factor. According to OPP officials, this allowed OPP to be consistent with the rest of the agency regarding setting RfDs, but still use the FQPA factor for regulating pesticides.

- OPP is concerned with both cancer and noncancer toxicity. However, for noncancer effects, OPP has paid special attention to neurotoxicity (because many pesticides work through this mechanism) and, more recently, to endocrine disrupting effects (those affecting the body's hormone system).[33]

- OPP officials noted that, while their agency has made important use of "real life" monitoring or incident data, it primarily relies on studies conducted in laboratory animals and on laboratory or limited field studies. They stated that, in their experience, "real life" data have profound limitations and that such data are inconsistent, expensive, inconclusive, and are not available for premarket decision making. They said that, most importantly, by the time there are observable health or environmental effects, it is too late to prevent the harm that could have been predicted from judicious use of animal or environmental fate studies conducted in the laboratory.

- During the exposure assessment step, OPP is concerned with a variety of routes, sources, and types of exposure. The three routes by which people can be exposed to pesticides are inhalation, dermal (absorbing

[33] Because of the potentially serious consequences of human exposure to endocrine disrupting chemicals, Congress included specific provisions on this topic in both the FQPA and the 1996 amendments to the Safe Drinking Water Act. In response to the FQPA language, EPA developed its Endocrine Disruptor Screening Program, which focuses on providing methods and procedures to detect and characterize endocrine activity of pesticides, commercial chemicals, and environmental contaminants. EPA uses a tiered approach for these risk assessments, sorting chemicals into four categories on the basis of the existing scientific data.

pesticides through the skin), and oral (getting pesticides in the mouth or digestive tract). Depending on the situation, a pesticide could enter the body by any one or all of these routes. Typical sources of pesticide exposure include food, home and personal use of pesticides, drinking water, and work-related exposure to pesticides (in particular, to pesticide applicators or vegetable and fruit pickers). In its approach to exposure assessment, OPP distinguishes between residential and occupational types of exposures. OPP officials noted that their program is further developing procedures to conduct drinking water exposure assessments and residential exposure assessments and that they have new procedures for ecological risk assessments.

- OPP calculates estimates of acute (i.e., short-term) pesticide exposure slightly differently from those for chronic (i.e., longer-term) exposures. This is because an acute assessment estimates how much of a pesticide residue might be consumed in a single day, while a chronic assessment estimates how much might be consumed on a daily basis over the course of a lifetime. In an important difference, acute assessments are based on high-end individual exposure assumptions, while chronic assessments use average exposure assumptions.

- In assessing both acute and chronic risks, OPP uses a tiered approach, starting with an initial screening tier and proceeding through progressively more elaborate risk assessments, if needed. The analytical tiers proceed from more conservative to less conservative assumptions. For the first-tier risk assessment, OPP uses "worst-case" assumptions (e.g., that pesticide residues are at tolerance levels and that 100 percent of the food crop is treated with the pesticide) that give only an upper-bound estimate of exposure. For more refined analyses, OPP officials noted that they have new procedures for conducting probabilistic dietary exposure assessments. Generally, the level of resources and the data needed to refine exposure estimates increase with each tier. Typically, if risks from pesticide residues are not of concern using lower-tier exposure estimates, OPP does not make further refinements through additional tiers. However, with the aggregate and cumulative exposure assessments now required by the FQPA, EPA notes that it is likely that higher-tier exposure estimates will be needed.

- The agency has developed procedures for modeling the environmental fate of pesticides. OPP officials said that these models use real data on the physical and chemical properties of the pesticide, information on the

proposed or actual uses of the pesticide, and real data on the movement of pesticides or other materials through soil, air, water, skin, textiles, or other media to predict potential exposures to a pesticide. These models are guided by scientific judgments that are based upon data and scientists' experience in drawing inferences from these data.

Office of Pollution Prevention and Toxics

OPPT (formerly the Office of Toxic Substances) is also part of OPPTS. OPPT was established to implement the Toxic Substances Control Act (TSCA), which authorizes EPA to screen existing and new chemicals used in manufacturing and commerce to identify potentially dangerous products or uses.[34] TSCA focuses on the properties of a chemical and paths of exposure to that chemical. Risk assessment activities are primarily related to four sections of TSCA:

- Section 4 directs EPA to require manufacturers and processors to conduct tests for existing chemicals when: (1) their manufacture, distribution, processing, use, or disposal may present an unreasonable risk of injury to health or the environment; or (2) they are to be produced in substantial quantities and the potential for environmental release or human exposure is substantial or significant. Under either condition, EPA must issue a rule requiring testing if existing data are insufficient to predict the effects of human exposure and environmental releases and testing is necessary to develop such data. Rhomberg pointed out that these conditions require OPPT to do some preliminary risk assessment and that, unlike testing mandates under other statutes (e.g., regarding pesticides), the agency has the burden of showing that such testing is necessary.[35]
- Section 5 addresses future risks through EPA's premanufacture screening—the premanufacture notification (PMN) process. This also applies to a "significant new use" of an existing chemical.
- Section 6 directs EPA to control unreasonable risks presented or that will be presented by existing chemicals.

[34] 15 U.S.C. 2601 *et seq.* In addition to its original role to implement TSCA, OPPT has been given responsibility for pollution prevention programs; regulation of specific toxic substances, including asbestos, radon, and lead; and administration of the Toxics Release Inventory.

[35]Lorenz Rhomberg, *A Survey of Methods for Chemical Health Risk Assessment Among Federal Regulatory Agencies*, a report prepared for the Presidential/Congressional Commission on Risk Assessment and Risk Management (1996).

- Section 8 requires EPA to gather and disseminate information about chemical production, use, and possible adverse effects to human health and the environment. This section requires EPA to develop and maintain an inventory of all chemicals, or categories of chemicals, manufactured or processed in the United States. All chemicals not on the inventory are, by definition, "new" and subject to the notification provisions of section 5. Once a chemical enters commerce through the section 5 process, it is listed as an existing chemical.

Although TSCA gives EPA general authority to seek out and regulate any "unreasonable risk" associated with new or existing chemicals, there are two major limitations on the agency's regulatory actions. First, as implemented by EPA, regulation under TSCA involves consideration of both risks and applying the least burdensome requirement needed to regulate the risk. The term "unreasonable risk" is not defined in TSCA. However, according to EPA, the legislative history indicates that unreasonable risk involves the balancing of the probability that harm will occur, and the magnitude and severity of that harm, against the effect of a proposed regulatory action on the availability to society of the expected benefits of the chemical substance. The second major limitation on EPA's authority under TSCA is a requirement to defer to other federal laws. Generally, if a risk of injury to health or the environment could be eliminated or reduced to a sufficient extent by actions taken under another federal law, that other law must be deferred to unless it can be shown to be in the public interest to regulate under TSCA.

The major distinction in the procedures that apply to OPPT risk assessments is between the evaluation of potential risks associated with exposures to new versus existing chemicals. For EPA to control the use of a chemical listed on the inventory of existing chemicals, according to OPPT, a legal finding has to be made that the chemical *will* present an unreasonable risk to human health or the environment. According to OPPT, this standard requires the agency to have conclusive data on that particular chemical. The agency noted, in comparison, that newly introduced chemicals (or uses) can be regulated under TSCA based on whether they *may* present an unreasonable risk, and this finding of risk can be based on data for structurally similar chemicals. Because industrial chemicals in commerce in 1975-1977 were "grandfathered" into the inventory without considering whether they were hazardous, there are situations in which existing chemicals might not be controlled, while EPA would act to control a new chemical of similar or less toxicity under the PMN program. Additional information on the major features and

characteristics of assessments for new versus existing chemicals is presented below.

Premanufacture notification for new chemicals or significant new uses

- TSCA requires manufacturers, importers, and processors to notify EPA at least 90 days prior to introducing a new chemical into the U.S. or undertaking a significant new use of a chemical already listed on the TSCA inventory. If available, test data and information on the chemical's potential adverse effects on human health or the environment are to be submitted to EPA. Much of this submission must be kept confidential by OPPT. However, there is no defined toxicity data set required before PMN, and, unless EPA promulgates a rule requiring the submission of test data, TSCA does not require prior testing of new chemicals. Consequently, according to EPA, less than half of the PMNs submitted include toxicological data. OPPT reviews approximately 1,500 PMNs annually.

- EPA has 90 days after notification to evaluate the potential risk posed by the chemical. EPA must then decide whether to (1) permit manufacture and distribution (the default if EPA takes no action), (2) suspend manufacture and distribution or to restrict use pending the development of further data, or (3) initiate rulemaking to regulate manufacture or distribution.

- OPPT typically has very limited chemical-specific data on toxic effects and exposure associated with new chemicals. When no data exist on the effects of exposure to a chemical, EPA may make its determination on what is known about the chemical's molecular structure (called the structure-activity relationship, or SAR) and the effects of other chemicals that have similar structures and are used in similar ways. OPPT's New Chemicals Program has issued a document entitled *Chemical Categories* that describes information for numerous classes of chemicals. In assessing exposures for new chemicals where exposure monitoring data are unavailable, OPPT uses several screening-level approaches, including (1) estimates based on data on analogous chemicals; (2) generic scenarios (i.e., standardized approaches for assessing exposure and release for a given use scenario); (3) mathematical models based on empirical and theoretical data and information; and (4) assumptions of compliance with regulatory limits, such as OSHA Permissible Exposure Limits (PELs).

- Rhomberg noted that OPPT cannot require full testing for all chemicals, because of statutory limitations under TSCA. He therefore characterized OPPT's assessments as "rough screens" designed to flag situations in which further testing should be required.

Assessments of existing chemicals

- Chemicals that OPPT assesses for regulation under sections 4 or 6 of TSCA are subject to a more rigorous risk assessment process. Compared to PMN reviews, such assessments are much more similar to those conducted elsewhere in EPA, so the EPA-wide guidelines generally apply.

- For hazard identification and dose-response assessment of carcinogens and noncancer effects, OPPT follows EPA-wide procedures. Because TSCA focuses on the properties of a chemical, rather than on a specific pathway or mode of exposure, OPPT considers the potential hazards posed through multiple routes of exposure. In lieu of information to the contrary, OPPT typically presumes that the results for one route are applicable to other routes.

- Similarly, in exposure assessment OPPT considers a variety of types and routes of exposure. Unlike other programs that focus on exposure through one medium, assessments under TSCA must assess all potential exposures to a chemical that may lead to unreasonable risk, considering, for example, both residential and occupational exposures. These risks may be assessed separately for each mode of exposure, even if occurring in the same setting. Overall, OPPT aims to provide both central estimates and upper-bound estimates of exposure, and it considers population risks as well as individual risks.

- OPPT shares overlapping concerns about a number of different kinds of exposure with other federal regulatory agencies. However, some aspects of OPPT's exposure assessments may differ from those of other programs or agencies concerned with similar exposures. For example, with regard to occupational exposures OPPT assumes that a working lifetime is 40 years, rather than the 45 years assumed by OSHA. Another example is the assumption of body weight; OPPT uses 70kg, whereas ORD recommends a value of 71.8 kg in its *Exposure Factors Handbook*.

In addition to the assessment of chemicals for regulation under sections 4 and 6 of TSCA, OPPT has recently launched a new program to voluntarily add screening-level hazard information on approximately 2,800 high-production-volume industrial chemicals and has proposed a second new voluntary program to address the risks of certain industrial chemicals to which children may be exposed. These two new programs operate under the same risk assessment processes used in the other OPPT programs noted above.

Office of Emergency and Remedial Response (Superfund Program)

OERR is part of EPA's Office of Solid Waste and Emergency Response (OSWER). Risk assessments are a required component of a larger remediation process established by 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).[36] Congress enacted CERCLA to facilitate the cleanup of hazardous waste sites. The act gave EPA broad authority to respond to releases of hazardous substances. SARA requires EPA to emphasize cleanup remedies that treat—rather than simply contain—contaminated waste to the maximum extent practicable and to use innovative waste treatment technologies.

Hazardous substances are defined by CERCLA to include substances identified under the Solid Waste Disposal Act, the Clean Water Act, the Clean Air Act, and the Toxic Substances Control Act, or designated by EPA. After investigating potentially hazardous sites, EPA ranks them according to the severity of their waste problems and places the worst on its National Priorities List for Superfund cleanup. Under CERCLA section 105, EPA uses a Hazard Ranking System to decide which sites to include on the list. Section 105 states that priorities are to be based upon relative risk or danger to public health or welfare or the environment, taking into account the population at risk, the hazard potential of the hazardous substances, and the potential for contamination of air and drinking water, among other factors.

OERR has developed a human health and environmental evaluation process as part of its remedial response program. Major features and characteristics of the Superfund risk assessment procedures are summarized below.

[36] 42 U.S.C. 9601-9675.

- Overall, the risk scenarios for Superfund can be very complex. Superfund sites are often associated with multiple potential pathways and routes of exposure, and mixtures of chemicals at Superfund sites are common. In addition, the Superfund program is required to consider ecological as well as human health risks.

- A risk assessment is performed after a particular site has been identified according to the National Contingency Plan, EPA's regulation outlining requirements relevant to response action(s) for hazardous substances. The remedial response process under the National Contingency Plan—and the role of risk information in the process—is summarized in the following seven steps:

  1. Site discovery or notification:
     - report determinations about which substances are hazardous.
  2. Preliminary assessment and site inspection:
     - collect and review all available information to evaluate the source and nature of hazardous substances.
  3. Hazard ranking system:
     - compile data from steps one and two in a numerical scoring model to determine a relative risk measure.
  4. Possible inclusion of site on the National Priorities List based on one of the following criteria:
     - the release scores sufficiently high pursuant to the Hazard Ranking System,
     - a state designates a release as its highest priority, or
     - the release satisfies all of the following criteria:
     - the Agency for Toxic Substances and Disease Registry has issued a health advisory that recommends dissociation of individuals from the release,[37]
     - EPA determines that the release poses a significant threat to public health, and

[37]The Agency for Toxic Substances and Disease Registry within the Department of Health and Human Services has an oversight role but no regulatory authority. It prepares "health assessments" rather than risk assessments that tend to be qualitative in nature, site specific, and focused on medical and public health perspectives. Exposures to site contaminants are presented in terms of sensitive populations, mechanisms of toxic chemical action, and possible disease outcomes. In contrast, EPA's human health evaluation, which is more quantitative, is a characterization of the potential for adverse effects from human exposures to environmental hazards.

- EPA anticipates that it will be more cost effective to use its remedial authority than to use removal authority to respond to the release.

5. Remedial investigation and feasibility study:
   - characterize the contamination at site where data is obtained to identify, evaluate, and select cleanup alternatives.
6. Selection of a remedy:
   - choose remedy that is protective of human health and the environment by eliminating, reducing, or controlling risks posed through each pathway, and
   - utilize risk information obtained during step five.
7. 5-year review.

One intended result of the remedial steps is the facilitation of a site-specific baseline risk assessment, designed to support risk management decision making. Human health and ecological risk assessments occur during step five, the Remedial Investigation/Feasibility Study stage.

- For human health risk assessments, Superfund procedures approximate the NAS paradigm, using the following four stages.

1. A data collection and evaluation stage that involves:
   - gathering and analyzing site data relevant to the human health evaluation, and
   - identifying substances present at the site that are the focus of the risk assessment process.
2. An exposure assessment that involves:
   - analyzing contaminant releases,
   - identifying exposed populations,
   - identifying potential exposure pathways and estimating exposure concentrations for pathways, and
   - estimating contaminant intakes for pathways.
3. A toxicity assessment stage that considers:
   - types of adverse health effects associated with chemical exposures,
   - relationships between magnitude of exposure and adverse effects,
   - related uncertainties such as the weight evidence of a particular chemical's carcinogenicity in humans, and
   - existing toxicity information developed through hazard identification and dose-response assessment.
4. A risk characterization that involves:
   - characterizing potential for adverse health effects (cancer or noncancer) to occur,

  - evaluating uncertainty, and
  - summarizing risk information.
- For ecological risk assessments, EPA's guidelines suggest that Superfund remedial actions generally should not be designed to protect organisms on an individual basis, but should protect local populations and communities of biota.[38] Furthermore, except for a few very large sites, Superfund ecological risk assessments typically do not address effects on entire ecosystems. Instead, they gather data regarding the effects on individuals in order to predict or postulate potential effects on local wildlife, fish, invertebrate, and plant populations and communities that occur or that could occur in specific habitats at sites (e.g., a wetland, floodplain, stream, estuary, or grassland). Specifically, the guidelines recommend that ecological risk assessments performed at every site follow an eight-step process:

1. Screening-level problem formulation and ecological effects evaluation:
   - site history,
   - site visit,
   - problem formulation, and
   - ecological effects evaluation.
2. Screening-level exposure estimate and risk calculation:
   - exposure estimate, and
   - risk calculation.
3. Baseline risk assessment problem formation:
   - ecotoxicity literature review,
   - exposure pathways,
   - assessment endpoints and conceptual model, and
   - risk questions.
4. Measurement endpoints and study design.
5. Verification of field sampling design.
6. Site investigation and data analysis.
7. Risk characterization.
8. Risk management.

- OERR uses a tiered approach for Superfund risk assessments, in which the agency employs more conservative methods and assumptions in the initial screening phases, followed by a more rigorous, multistage risk assessment if screening results indicate the need. Under Superfund,

[38] An exception would be actions affecting designated protected status resources that could be exposed to site releases. Such resources include treaty-protected species and species that are listed as or candidates for threatened or endangered status.

decisions generally are made on a site-by-site basis. According to agency officials, early activities at Superfund sites are often based on initial tier screening. However, they pointed out that the remedial cleanup decision is supported by a site-specific risk assessment that is usually quite detailed with either site-specific exposure assumptions or national default assumptions appropriate to the site which result in "high-end" reasonable risk estimates. Although the Superfund program initially employed an approach of using a hypothetical "worst case" scenario for exposure assessments, EPA's exposure assessment guidance now emphasizes use of a more realistic upper-bound exposure scenario. The EPA guidelines emphasize that this exposure scenario should be in the range of plausible real exposures, and also call for a central tendency case. In addition, guidelines put forth by the Superfund program office emphasize streamlining the process and reducing the cost and time required, focusing on providing information necessary to justify action and select the best remedy for a Superfund site. In doing so, Superfund guidelines suggest using standardized assumptions, equations, and values wherever appropriate.

- The Superfund program uses extensive additional program-specific guidance documents addressing human health and ecological risk assessments, as well as analytical tools, such as probabilistic analysis. These documents supplement applicable EPA-wide guidelines. The Superfund guidelines for human health risk assessment, for example, cover developing a baseline risk assessment (Part A), developing or refining preliminary remediation goals (Part B), performing a risk evaluation of remedial alternatives (Part C), and standardizing, planning, reporting, and completing a review (Part D). There are also other headquarters and regional office documents that further supplement the program-specific guidelines and manuals.

Office of Solid Waste

The Office of Solid Waste, like OERR, is part of OSWER. OSW regulates the management of solid waste and hazardous waste through federal programs established by the Resource Conservation and Recovery Act of 1976, as amended (RCRA).[39] Congress enacted RCRA to protect human health and the environment from the potential hazards of waste disposal, conserve energy and natural resources, reduce the amount of waste generated, and ensure that wastes are managed in a manner that is protective of human health and the environment. The act defines solid and hazardous waste,

[39] 42 U.S.C. 6901-6991k.

authorizes EPA to set standards for facilities that generate or manage hazardous waste, and establishes a permit program for hazardous waste treatment, storage, and disposal facilities. The RCRA hazardous waste program has a "cradle to grave" focus, regulating facilities that generate, transport, treat, store, or dispose of hazardous waste from the moment it is generated until its ultimate disposal or destruction.

RCRA regulations interact closely with other environmental statutes, especially CERCLA. EPA notes that both programs are similar in that they are designed to protect human health and the environment from the dangers of hazardous waste, but each has a different regulatory focus. RCRA mainly regulates how wastes should be managed to avoid potential threats to human health and the environment. On the other hand, according to EPA, CERCLA is relevant primarily when mismanagement occurs or has occurred, such as when there has been a release or a substantial threat of a release in the environment of a hazardous substance.

Regulatory activity under RCRA focuses primarily on specifying procedures and technology to be used to ensure proper handling and disposal of wastes, but risk assessments play a role in several supporting tasks, particularly those involving hazardous waste regulation under RCRA Subtitle C. For example, risk assessment information may be used in the processes for defining (and delisting) substances as hazardous wastes, evaluating the hazards posed by waste streams, assessing the need for corrective action at disposal sites, and granting waste disposal permits (such as incinerator permits). In its *RCRA Orientation Manual*, OSW expressed an increasing emphasis on making the RCRA hazardous waste program more risk based (with the intention of ensuring that the regulations correspond to the level of risk posed by the hazardous waste being regulated). Major features and characteristics of risk assessment for hazardous waste regulation are summarized below.

- Making the determination of whether a substance is a hazardous waste is a central component of the waste management program. The Subtitle C program includes procedures to facilitate this identification and classification of hazardous waste. Under the RCRA framework, hazardous wastes are a subset of solid wastes.[40] In RCRA §1004(5), Congress defined hazardous waste as a solid waste, or combination of

[40] Despite the name, solid wastes actually may be solids, semi-solids, liquids, or sludges.

solid wastes, which because of its quantity, concentration, or physical, chemical, or infectious characteristics may:

- cause, or significantly contribute to, an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness; or
- pose a substantial present or potential hazard to human health or the environment when improperly treated, stored, transported, or disposed of, or otherwise managed.

EPA developed more specific criteria for defining hazardous waste using two different mechanisms: (1) listing certain specific solid wastes as hazardous and (2) identifying characteristics (physical or chemical properties) which, when exhibited by a solid waste, make it hazardous. The agency has done so, and risk assessment information may be used to support both mechanisms.[41]

- "Listed wastes" are wastes from generic industrial processes, wastes from certain sectors of industry, and unused pure chemical products and formulations. EPA uses four criteria to decide whether or not to list a waste as hazardous.

1. The waste typically contains harmful chemicals (and exhibits other factors, such as risk and bioaccumulation potential) which indicate that it could pose a threat to human health and the environment in the absence of special regulation. Such wastes are known as toxic listed wastes.

2. The waste contains such dangerous chemicals that it could pose a threat to health or the environment even when properly managed. These wastes are fatal to humans and animals even in small doses and are known as acute hazardous wastes.

3. The waste typically exhibits one of the four characteristics of hazardous waste: ignitability, corrosivity, reactivity, and toxicity.

4. EPA has cause to believe that, for some other reason, the waste typically fits within the statutory definition of hazardous waste.

[41] In addition, there are some wastes that are specifically excluded from Subtitle C regulation and wastes that may be exempted when recycled.

Listed hazardous wastes can exit Subtitle C regulation through a site-specific delisting process initiated by a petition from a waste handler to an EPA region or a state. The petition must demonstrate that, even though a particular waste stream generated at a facility is a listed hazardous waste, it does not pose sufficient hazard to merit RCRA regulation.

- "Characteristic wastes" are wastes that exhibit measurable properties that indicate they pose enough of a threat to deserve regulation as hazardous wastes. EPA established four hazardous waste characteristics.

1. Ignitability identifies wastes that can readily catch fire and sustain combustion.

2. Corrosivity identifies wastes that are acidic or alkaline. Such wastes can readily corrode or dissolve flesh, metal, or other materials.

3. Reactivity identifies wastes that readily explode or undergo violent reactions (e.g., when exposed to water or under normal handling conditions).

4. Toxicity is used in a rather narrow and specific sense under this program to identify wastes that are likely to leach dangerous concentrations of chemicals into ground water if not properly managed (and thus expose users of the water to hazardous chemicals and constituents).

EPA developed a specific lab procedure, known as the Toxicity Characteristic Leaching Procedure, to predict whether any particular waste is likely to leach chemicals into ground water at dangerous levels. In this procedure, liquid leachate created from hazardous waste samples is analyzed to determine whether it contains any of 40 different common toxic chemicals in amounts above specified regulatory levels. The regulatory levels are based on ground water modeling studies and toxicity data that calculate the limit above which these toxic compounds and elements will threaten human health and the environment.

- For OSW, the task of identifying and assessing hazardous wastes is made more difficult because waste may be in the form of a mixture of constituents, some of which may be hazardous and some not. (This is also a common issue for the Superfund program.) The EPA-wide guidelines on assessments of chemical mixtures therefore could come

into play in OSW risk assessments.

- For dose-response data on the toxicity and potency of hazardous substances, OSW largely relies on information from other EPA sources. For example, OSW may use the chemical-specific assessments prepared by ORD, data in EPA's IRIS database, and regulatory standards from other EPA program offices, in particular the Office of Water. However, OSW combines this information with its own exposure analyses.

- Rhomberg categorized exposure assessment by OSW as either hypothetical or site specific. He noted that hypothetical exposures principally come into play when the agency is defining hazardous wastes and evaluating disposal options. These exposure analyses cover hypothetical waste-handling and disposal practices anywhere in the nation, and OSW focuses on the question of whether such practices might cause undue risks to individuals, not on characterizing the actual distribution of exposures across the population. One of the principal concerns in OSW exposure assessments is leaching to groundwater, but OSW evaluates other exposure pathways from virtually all treatment and disposal practices, with the specific pathways for any particular analysis being decided on a case-by-case basis. Site-specific exposure assessments might be needed when OSW is making regulatory decisions regarding actual waste disposal facilities, as when assessing the need for remedial action at a given site or permitting incineration or other disposal activities. In such cases, the office can focus exposure estimates on the off-site migration of the particular toxic compounds associated with that location. In general, an important part of OSW's exposure assessments is evaluating the "relative contribution" of hazardous wastes to the overall exposure to a hazardous chemical (which is very similar to assessments by EPA's Office of Water).

- In exposure assessments, OSW's deterministic analyses follow EPA's risk characterization guidance by setting only two sensitive parameters at high-end values, with the rest of the parameters being set at their central tendency values. According to OSW, this approach is meant to produce a risk estimate above the 90th percentile of the risk distribution but still on the actual distribution.

Chemical Emergency Preparedness and Prevention Office

CEPPO is also part of OSWER. It provides leadership, advocacy, and assistance to: (1) prevent and prepare for chemical emergencies; (2) respond to environmental crises; and (3) inform the public about chemical hazards in their community. To protect human health and the environment,

CEPPO develops, implements, and coordinates regulatory and nonregulatory programs. It carries out this work in partnership with EPA regions, domestic and international organizations in the public and private sectors, and the general public.

CEPPO is responsible for the risks associated with accidental chemical releases. Under the Emergency Planning and Community Right-to-Know Act (EPCRA) in Title III of the Superfund Amendments and Reauthorization Act of 1986, CEPPO must evaluate, develop, and maintain a list of chemicals and threshold quantities that are subject to reporting for emergency planning. In addition, CEPPO develops the emergency reporting and planning requirements, guidance for industry, and guidance and tools for use of the reporting information by Local Emergency Planning Committees. These reporting and planning requirements serve to provide the necessary information to be used at the local level to manage the risks associated with accidental chemical releases.

CEPPO is also responsible for accidental chemical release prevention. Under Section 112(r) of the Clean Air Act, as amended by the Clean Air Act Amendments of 1990, CEPPO must evaluate chemicals for acute adverse health effects, likelihood of accidental release, and magnitude of exposure to develop a list of at least 100 substances that pose the greatest risk of causing death, injury, or serious adverse effects to human health or the environment from accidental releases. Each listed substance must have a threshold quantity that takes into account the chemical's toxicity, reactivity, volatility, dispersability, combustibility, or flammability.

Facilities handling a listed substance above its threshold quantity must implement a risk management program and develop a risk management plan. The risk management program must address a hazards analysis, prevention program, and emergency response program. According to CEPPO officials, they scaled these regulatory requirements according to the risk posed by the wide range of facilities subject to the requirements—the greater the risk, the greater the risk management responsibilities. The facilities submit their risk management plans to EPA and to state and local officials for use in emergency planning and local risk management and reduction. CEPPO investigates chemical accidents, conducts research, and collects information about chemical and industrial process hazards to issue Chemical Safety Alerts and other publications to raise awareness about chemical accident risks. CEPPO also develops tools, methods, and guidance necessary to identify and assess the risks to human health from accidental releases.

Major features and characteristics of CEPPO's risk assessment procedures are summarized below.

- The chemical risk assessments conducted by CEPPO are unique from the risk assessments conducted by other EPA offices. CEPPO's procedures do not follow the NAS four-step risk assessment approach, but are similar to the chemical risk assessment approach used by the Department of Transportation's (DOT) Research and Special Programs Administration (RSPA) in that hazards are identified and a measure of exposure (or consequence) is determined to yield a "threat" associated with an accidental release. While RSPA focuses on risks associated with accidents involving unintentional releases of hazardous materials during transportation, CEPPO focuses on risk associated with accidental releases from a fixed facility. According to CEPPO, for accidental release risks, because these events are high consequence and low probability, the hazard and exposure typically can be estimated with some degree of confidence. However, the likelihood or probability of an accidental release is very uncertain. Consequently, likelihood is addressed only in a limited way and the "threat" is judged to be a surrogate for risk.

- CEPPO's approaches with respect to chemical accident risk are published mainly in two rulemakings—"List of Regulated Substances and Thresholds for Accidental Release Prevention and Risk Management Programs for Chemical Accident Release Prevention," 59 FR 4478 (Jan. 31, 1994) and "Accidental Release Prevention Requirements: Risk Management Programs under the Clean Air Act, Section 112(r)(7)," 61 FR 31668 (June 20, 1996)—and in guidelines, especially "Technical Guidance for Hazards Analysis, Emergency Planning for Extremely Hazardous Substances," which was issued jointly by EPA, DOT, and the Federal Emergency Management Agency (Dec. 1987).

- For hazard identification, CEPPO identifies the hazards that pose a risk to human health and the environment from an analysis of chemical accidents and of the physical/chemical properties of substances that make them more likely to cause harm as a result of an accidental chemical release. For example, the catastrophic chemical release in Bhopal, India, in December 1984 involved methyl isocyanate, a chemical that is toxic when inhaled. CEPPO identified the criteria necessary to identify those substances that are so toxic that, upon exposure (i.e., inhalation, dermal contact, or ingestion) to a small amount, they cause

death or serious irreversible health effects in a short time (acute toxicity). CEPPO also has developed criteria to identify other substances, such as highly flammable substances that can trigger a vapor cloud explosion harming the public and environment. CEPPO is also working to understand the long-term (chronic) effects that might be generated by a single acute exposure.

- As part of its identification of hazards, CEPPO also evaluates the quantity of a chemical that would need to be released and travel off-site to establish a threshold quantity.[42] If a facility handles more than this quantity, there is a presumption of risk triggering some action by the facility's owner(s) and operator(s). The hazardous chemicals and threshold quantities identified by CEPPO are published in rulemakings.

- According to CEPPO, the exposure assessment (or consequence analysis) phase of a chemical accident release assessment is somewhat unique from the classical risk assessment approaches and procedures. The actual exposure to humans after an accidental release is often not known. In addition, the amount and rate of chemical released and the precise conditions (e.g., weather) are usually not known. However, these parameters can be estimated using engineering calculations and mathematical models to generate the concentration likely to have been present or that could be present in a certain type of accidental release. Using these techniques, chemicals that possess the physical/chemical properties most likely to harm the public or the environment can be evaluated to estimate the degree of "threat" that they may pose in an accidental release.

- CEPPO uses these exposure assessment (consequence analysis) techniques to understand the potential magnitude of exposure associated with a variety of hazardous chemicals. In addition, CEPPO publishes the techniques in guidelines and as software to assist facilities in their assessment of accidental release risk. According to CEPPO, industry has a fundamental responsibility to understand the risks associated with chemical accidents. In addition, the Risk Management Plan requirements under section 112(r) of the Clean Air Act require that this information be made available to the public so that industry and the

[42] A CEPPO official pointed out that his agency's focus is the general public and environment outside the bounds of an industrial facility. The Occupational Safety and Health Administration is responsible for risk within the bounds of an industrial facility.

community can work together to manage the risks that might be present.

- CEPPO may characterize the risks associated with accidental releases using a number of parameters, such as the presence of a large quantity of a highly hazardous substance in proximity to a large facility that has had a number of accidental releases in the past. CEPPO uses these parameters to place more responsibility on such facilities (e.g., greater accidental release prevention measures under the Risk Management Program requirements), to investigate the underlying reasons for their accidental releases, or to assist in audits and inspections of their accident prevention programs.

Office of Air and Radiation

OAR oversees the air and radiation protection activities of the agency. Radiation risk assessments conducted by OAR are outside the scope of this report, but chemical risk assessments do have a part in OAR's efforts to preserve and improve air quality in the United States.[43] Such air quality concerns are the primary mission of OAR's Office of Air Quality Planning and Standards (OAQPS), which, among other activities, compiles and reviews air pollution data and develops regulations to limit and reduce air pollution. The Risk and Exposure Assessment and the Health and Ecosystem Effects Groups within OAQPS provide the scientific and analytical expertise to conduct and support human health and ecological risk assessments in this area, in coordination with ORD.

The Clean Air Act, as amended, provides the statutory basis for air-related risk assessments by OAR.[44] The CAA requires EPA to establish national standards for air quality, but it gives states the primary responsibility for assuring compliance with the standards. Chemical risk assessments are primarily associated with regulation of (1) criteria air pollutants and (2) hazardous air pollutants, also referred to as "air toxics."[45]

[43] See *Radiation Standards: Scientific Basis Inconclusive, and EPA and NRC Disagreement Continues* (GAO/RCED-00-152, June 30, 2000) for information regarding some of the procedures used by EPA in setting radiation standards.

[44] 42 U.S.C. 7401-7626.

[45] There are other distinct programs within OAR—for example, focusing on the regulation of mobile sources (including fuels and fuel additives), acid rain, and global climate change—that also include consideration of chemicals.

The CAA requires EPA to set health-based air quality standards (National Ambient Air Quality Standards, or NAAQS) for criteria pollutants, which are common throughout the United States and mostly the products of combustion.[46] Under the CAA, EPA is also required to review the scientific data upon which the standards are based and revise the standards, if necessary, every 5 years. The criteria pollutants are particulate matter, carbon monoxide, sulfur oxides, nitrogen dioxide, ozone, and lead. Of these pollutants, ozone is not directly emitted by a source, but rather is the product of the interaction of nitrogen oxide, volatile organic compounds, and sunlight. Therefore, regulations targeting ozone focus on controlling emissions of nitrogen oxide and volatile organic compounds. The CAA requires EPA to set health-based standards with an "adequate margin of safety," but according to EPA it is not required to set air quality standards at a zero-risk level to achieve an adequate margin of safety, but simply at a level that avoids unacceptable risks. EPA therefore sets the standards to protect the substantial part of the national population, including sensitive or at-risk populations, but not necessarily the most sensitive or exposed individuals.

The CAA also contains provisions, first added in 1970, for the regulation of emissions to the atmosphere of hazardous air pollutants—toxic chemicals other than the six criteria pollutants. The 1970 amendments to the CAA required EPA to identify and control hazardous air pollutants so as to achieve "an ample margin of safety." However, Congress passed another major set of amendments, the Clean Air Act Amendments of 1990 (CAAA), which revised the hazardous air pollutant provisions and substantially affected the application of risk assessment regarding air toxics. The amendments explicitly wrote into the act a list of 189 hazardous air pollutants to be regulated. In addition, the amendments replaced the former health-based criterion for standards with a criterion that is primarily technology based, mandating the maximum achievable control technology (MACT) for the specified list of chemicals.[47] The act further mandates that EPA evaluate residual risks remaining after implementation

[46] The states are responsible for establishing procedures to attain and maintain the standards. They prepare State Implementation Plans (SIPs) on these procedures that are submitted to EPA for approval.

[47] All new or existing sources of these pollutants are to require the use of MACT, which is judged to be "the best of the best" for new sources and at the top end (best 12 percent) of current emissions control performance for existing sources.

of the MACT standards to determine if additional standards are needed to protect the public health with an ample margin of safety.

Additional information on the major features and characteristics of chemical risk assessments related to these air quality protection activities is presented below.

Criteria air pollutants

- There are several unique features that affect risk assessments for criteria air pollutants. Compared to many other agents assessed by EPA, the agency generally has extensive human data available on health effects at relevant exposure levels. Therefore, risk assessments for criteria air pollutants require little extrapolation across species or to low doses and few default assumptions. These are the least likely of EPA's risk assessments to use precautionary or conservative methods and assumptions, and the results are intended to be unbiased estimates without any built-in conservatism.

- For criteria air pollutants, "hazard identification" information on health effects appears primarily in air quality criteria documents prepared by ORD and staff papers prepared by OAQPS to support the review and development of national ambient air quality standards. These documents are intended to reflect the available scientific evidence on toxicity endpoints of concern. The definition of what responses constitute "adverse" outcomes is ultimately left to the Administrator's judgment, informed by staff recommendations, advice from the Clean Air Scientific Advisory Committee (part of EPA's Science Advisory Board), and public comments.

- EPA's principal concern regarding criteria pollutants is for noncancer health effects. In contrast to most other EPA noncancer risk assessments, however, EPA does not apply a threshold approach in the case of criteria pollutants. Instead, the agency models response curves as though they have no threshold, recognizing that, as a practical matter, at least some members of the general population will have their thresholds exceeded at or near the lowest exposure levels. EPA characterizes these response relationships without any conservative upper-bound methods. However, probabilistic methods are used to characterize uncertainty in the fitted exposure-response relationships. In addition, there is temporal variation in pollution concentrations, so characterization of exposure-time relationships is also an important

component of EPA's assessments of criteria pollutants.

- Although EPA's exposure assessments (and risk characterization) for criteria pollutants focus on population risks, rather than individual risks, the agency does consider effects on more sensitive or exposed populations. Exposure assessments are also affected by the need to establish air quality standards for both annual and daily concentrations for some pollutants. The annual standards are intended to provide protection against typical day-to-day exposures as well as longer-term exposures, while the daily standards are intended to provide protection against days with high peak concentrations of pollutants. EPA's exposure assessments therefore need to address these types of variations. Rhomberg noted that, because of the long history of analysis of standard pollutants, EPA's exposure modeling has been continually improved and expanded, resulting in sophisticated models with capabilities well beyond models used in other situations that do not have the benefit of decades of experience and application.

- Finally, it is important to recognize that one of the most important uses of risk assessments regarding criteria air pollutants is to characterize the population exposure levels and health effects that would be expected given various specified air quality criteria. In other words, one of the primary uses of risk assessment is to estimate what the effects would be if standards were set at various specified levels, rather than using the tool simply to estimate what health risks these pollutants pose.

Hazardous air pollutants (air toxics)

- Although the Clean Air Act Amendments of 1990 shifted the focus in hazardous air pollutant regulation to technology-based controls, several activities may still involve risk assessments, including
  - listing and delisting of hazardous air pollutants, which depends on whether a chemical may present a threat of adverse effects to humans and the environment;
  - *de minimis* delisting of source categories, which requires sources be listed unless they pose less than a 10^{-6} risk to the maximally exposed individual (MEI);
  - triggering the consideration of further regulation to address residual risks that remain after applying MACT standards (triggered if the MEI suffers a 10^{-6} or greater lifetime risk); and

- offset trading of one pollutant for another based on whether the increase in emissions is offset by an equal or greater decrease in a "more hazardous" air pollutant.

- According to section 112(o) of the amended CAA, prior to the promulgation of any residual risk standard, EPA shall revise its guidelines for carcinogen risk assessment or provide an explanation of the reasons regarding any NAS report section 112(o)(4) recommendations that have not been implemented.

- The amended act also had a major impact on hazard identification for air toxics. The amendments defined hazardous air pollutants as air pollutants listed pursuant to section 112(b) of the act. Section 112(b) included an initial list of 189 compounds incorporated by reference into the law.

- Dose-response analysis for air toxics has in the past been done largely through Health Assessment Documents produced by ORD for the air office, according to the methods discussed in the earlier section on EPA-wide risk assessment procedures. Carcinogen potency calculations for *de minimis* delisting and residual risk determination will be done under the revised carcinogen assessment guidelines, once they are finalized. EPA addresses noncancer risks for hazardous air pollutants with its usual methodologies (e.g., NOAEL/LOAEL, benchmark dose, or others).

- With the 1990 amendments, exposure assessments for air toxics will focus on assessing the residual risk for the most exposed individual after MACT has been applied. OAR uses a population-based risk assessment to generate estimates of how risks are distributed within the population, not just for specific conservative scenarios. According to Rhomberg (and confirmed by OAR officials), OAR's intent is to define the actual most exposed person in the population, rather than a hypothetical person with an unrealistically high estimated exposure. EPA has adopted a tiered approach to analyzing residual risk consistent with the recommendations from NAS and the Presidential/Congressional Commission.[48] In the screening phase, default conservative assumptions are used to ensure that risks will not be underestimated. Sources and hazardous air pollutants that exceed some benchmark in the screening analysis will be evaluated further. According to OAR, the more refined assessments will utilize more site-specific information and more realistic assumptions, especially as they relate to exposure. EPA estimates exposures to air toxics using a general-purpose model largely based on fate and transport considerations for stack emissions.[49] OAR officials noted that they are updating their modeling methodology, updating their Human Exposure Model with the current state-of-the-art dispersion model (ISCST3), and will be updating the census data they use with the 2000 Census numbers when they become available.

Office of Water

OW is responsible for the agency's water quality activities, including development of national programs, technical and science policies, regulations, and guidance relating to drinking water, water quality, ground water, pollution source standards, and the protection of wetlands, marine, and estuarine areas. Chemical risk assessments are associated, in particular, with EPA's ambient water quality criteria, under the CWA, and drinking water quality regulations, under the SDWA.[50]

The goal of CWA is to maintain and improve the cleanliness and biological integrity of the nation's waters, including lakes, rivers, and navigable waters. Under CWA, EPA publishes water quality criteria defining the

[48] See *Residual Risk Report to Congress*, U.S. EPA (March 1999).

[49] Fate and transport models are mathematical descriptions of the movement and transformation of substances through various media, such as air, soil, and water.

[50] CWA is codified generally as 33 U.S.C. 1251-1387 and SDWA as 42 U.S.C. 300f-300j.

degree of water quality that is compatible with intended uses and states of different water bodies. The criteria are health based, but they are not rules and are themselves unenforceable. States use these criteria as guidance for developing state water quality standards and setting enforceable limits in permits for facilities that discharge pollutants into surface waters. CWA distinguishes "conventional" from "toxic" pollutants. Toxic water pollutants are evaluated as exposures to toxic chemicals (similar to EPA's treatment of hazardous air pollutants).

The goal of SDWA is to protect the quality of public drinking water systems. The law focuses on all waters actually or potentially designed for drinking use, whether from above ground or underground sources. SDWA requires EPA to set drinking water standards to control the level of contaminants in drinking water provided by public water systems, which the water systems are required to meet.[51] Congress passed extensive amendments to SDWA through the Safe Drinking Water Act Amendments of 1996 (PL 104-182). Among other key changes, the amendments increased regulatory flexibility, focused regulatory efforts on contaminants posing the greatest health risks, and added risk assessment and risk communication provisions to SDWA.

There are several risk-related mandates in these acts.

- Under CWA, EPA is to establish criteria for water quality solely on the basis of health and ecological effects and "accurately reflecting the latest scientific knowledge… on the kind and extent of all identifiable effects on health and welfare." CWA defines a toxic pollutant as one that after discharge and upon exposure, ingestion, inhalation, or assimilation into any organism, either directly from the environment or indirectly by ingestion through food chains, will, on the basis of information available to the Administrator, cause death, disease, behavioral abnormalities, cancer, genetic mutations, physiological malfunctions (including malfunctions in reproduction), or physical deformities in such organisms or their offspring. Federal water quality criteria are unenforceable, but states develop enforceable permit limits

[51] Drinking water standards apply to public water systems that provide water to at least 15 connections used by year-round residents or regularly serve at least 25 year-round residents. Private water wells serving fewer than 25 persons are not covered by these federal standards. EPA also sets Secondary Drinking Water Regulations, which are nonenforceable guidelines for contaminants that may cause cosmetic or aesthetic effects.

based on them.

- In contrast to the unenforceable federal water quality criteria, CWA also provides for the promulgation of enforceable federal performance standards for sources of effluent (waste discharged into a river or other water body) that do include consideration of technological and economic feasibility. Since 1977, establishment of effluent standards for toxic pollutants has been based on the best available technology (BAT) economically achievable by particular source category. The compounds to be regulated are specified in a list, and there are provisions for additions and deletions to the list. Standards must be at that level which the Administrator determines provides "an ample margin of safety," so that standards more stringent than BAT may be named at EPA discretion.

- Under SDWA, the EPA Administrator is to "promulgate national primary drinking water regulations for each contaminant… which… may have any adverse effect on the health of persons and which is known or anticipated to occur in public water systems." An important feature of such regulations, however, is that a standard specifies two levels of contamination. First, a maximum contaminant level goal (MCLG) is set solely on health grounds "at a level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." For each such goal there is also a maximum contaminant level (MCL). This MCL is to be as close to the MCLG "as is feasible," where feasible means "with the use of the best technology, treatment techniques and other means which… are available (taking cost into consideration)." The MCL is the enforceable standard.

- The 1996 amendments to SDWA added several provisions that increased the importance of risk assessment and risk communication in EPA's regulation of drinking water quality. For example, the amendments
  - Require EPA, when developing regulations, to (1) use the best available, peer-reviewed science and supporting studies and data and (2) make publicly available a risk assessment document that discusses estimated risks, uncertainties, and studies used in the assessment.
  - Require EPA to conduct a cost-benefit analysis for every new standard to determine whether the benefits (health risk reduction) of a drinking water standard justify the costs.
  - Permit consideration of "risk-risk" issues by authorizing EPA to set a standard other than the feasible level if the feasible level would lead

to an increase in health risks by increasing the concentration of other contaminants or by interfering with the treatment processes used to comply with other SDWA regulations.
- Require EPA to review and revise, as appropriate, each national primary drinking water regulation promulgated by the agency at least every 6 years. Of particular relevance to the use of risk assessment information, any revisions must "maintain, or provide for greater, protection of the health of persons."
- Require EPA to identify subpopulations at elevated risk of health effects from exposure to contaminants in drinking water and to conduct studies characterizing health risk to sensitive populations from contaminants in drinking water.

Additional information on major features and characteristics of chemical risk assessments related to water quality protection activities is presented below.

- The various offices within OW—the Office of Ground Water and Drinking Water; Office of Science and Technology; Office of Wastewater Management; and Office of Wetlands, Oceans, and Watersheds—have developed extensive technical and analytical guidance on water quality monitoring and the development of water quality criteria. One recently finalized document particularly relevant for describing OW's current risk assessment procedures is the revision to the methodology for deriving ambient water quality criteria (AWQC) for the protection of human health.[52] Published pursuant to section 304(a)(1) of the CWA, OW noted that this revised methodology supersedes EPA's 1980 guidelines and methodology on this subject. In addition to describing OW's approach to developing new and revising existing AWQC, it defines the default factors that EPA will use in evaluating and determining consistency of state water quality standards with the requirements of the CWA.

- Although there are different statutory bases and risk mandates for the regulation of ambient and drinking water, OW's risk assessment procedures in support of CWA and SDWA are mostly similar.

[52] *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health*, also referred to as the "2000 Human Health Methodology," EPA-822-B-00-005 (October 2000). The agency is also in the process of revising its methodology for deriving AWQC for the protection of aquatic life.

However, risk assessments in support of CWA consider not just human health effects but also the ecological effects associated with exposure to pollutants. With regard to human health risks, perhaps the most notable difference between the ambient water and drinking water parts of OW is the additional focus, during exposure assessments for CWA purposes, on exposures to contaminated water through consumption of contaminated fish or shellfish. (This is a primary reason for potential differences in the resulting drinking water and ambient water quality criteria or standards for the same chemical.)

- OW's Office of Science and Technology does all of the risk assessments for SDWA maximum contaminant level goals and CWA's AWQC. For cancer risk evaluation, OW has been applying the principles in EPA's proposed revision of the carcinogen guidelines.

- For hazard identification purposes, SDWA originally had specified a list of compounds to be regulated as toxic pollutants and required EPA to regulate an additional 25 contaminants every 3 years. However, the 1996 amendments eliminated that requirement and revised OW's approach for listing, reviewing, and prioritizing the drinking water contaminant candidate list. The new risk-based contaminant selection process provides EPA the flexibility to decide whether or not to regulate a contaminant after completing a required review of at least five contaminants every 5 years. EPA must use three risk-related criteria to determine whether or not to regulate: (1) that the contaminant adversely affects human health; (2) it is known or substantially likely to occur in public water systems with a frequency and at levels of public health concern; and (3) regulation of the contaminant presents a meaningful opportunity for health risk reduction. The 1996 amendments also included specific requirements to assess health risks and set standards for arsenic, sulfate, radon, and disinfection byproducts.

- There are a number of important features regarding OW's exposure assessments in support of CWA and SDWA regulations.

  - OW's primary exposure question during the criteria/standard-setting process for drinking or ambient water is hypothetical: What health effects might be expected if people consumed water and/or finfish and shellfish contaminated at the level of a candidate standard? The main function of exposure assessment is to link criteria or water

concentrations to doses of chemicals and the associated health effects that might be projected.

- For its exposure assessments, OW uses estimates of water and food ingestion in the United States based on a variety of surveys and studies. One of the major sources of per capita water and fish ingestion is the Department of Agriculture's Continuing Survey of Food Intakes by Individuals (CSFII), which presents results for the general population and for certain subpopulations (e.g., pregnant and lactating women, children).[53]

- For assessing standards under SDWA, the linking of water concentration to dose is conducted through standardized consumption values. For example, the default exposure scenario of lifetime consumption by individuals is 2 liters of water per day. However, OW uses other default values to address consumption by sensitive subpopulations, especially children and infants. For assessing AWQC under the CWA, EPA uses the same water consumption rate as under SDWA. In addition, though, the agency adds the dose resulting from the daily average consumption of 17.5 grams of fish.

- An important change in EPA's approach for developing AWQC, reflected in the *2000 Human Health Methodology*, has been the move toward use of a bioaccumulation factor (BAF) to estimate potential human exposure to contaminants via the consumption of contaminated fish and shellfish. BAFs reflect the accumulation of chemicals by aquatic organisms from all surrounding media (e.g., water, food, and sediment). EPA's 1980 method used a bioconcentration factor that reflected only absorption directly out of the water column, and therefore tended to underestimate actual contaminant levels in fish and shellfish. EPA's revised methodology also gives preference to the use of high-quality field data over laboratory or model-derived estimates of BAFs.

- OW considers indirect exposures to a substance from sources other than drinking water (e.g., food and air) when establishing AWQC. This is particularly important for noncarcinogens, where the fact that

[53] The CSFII is a complex multistage probability sample of the entire United States conducted to survey food and beverage intake.

several exposure sources might individually be below the RfD level does not mean that collectively the exposure is below this presumably safe level. OW has revised and expanded its policy on accounting for nonwater sources of indirect exposures known as the "relative source contribution." The procedures for calculating the relative source contribution vary depending on the adequacy of available exposure data, levels of exposure, sources and media of exposure relevant to the pollutant of concern, and whether there are multiple health-based criteria or standards for the same pollutant. (See table 5 in the next section for a more detailed description of these assumptions.)

Risk Assessment Assumptions and Methodological Choices

EPA's risk assessment guidelines and other related documents identify many default assumptions, standardized data factors, and methodological choices that may be used in chemical risk assessments. As pointed out by NAS, assumptions and professional judgment are used at every stage of a risk assessment, because there are always uncertainties in risk assessments that science can not directly answer. For the most part, these assumptions and choices are intended to address various types of uncertainties—such as an absence or limited amount of available data, model uncertainty, and gaps in the general state of scientific knowledge—or variability in the population. They are also intended to provide some consistency and transparency to agency risk assessments. Defaults are generally used in the absence of definitive information to the contrary, but also reflect policy decisions.

In its guidelines, EPA characterizes many of its choices as conservative or public-health protective in that they are intended to help the agency avoid underestimating possible risks. Agency guidelines often cited the scientific studies and other evidence that supported the agency's choice and the plausibility of the resulting risk estimates. In our recent report on EPA's use of precautionary assumptions, we identified three major factors influencing the agency's use of such assumptions: (1) EPA's mission to protect human health and safeguard the natural environment (including specific requirements in some of the underlying environmental statutes), (2) the nature and extent of relevant data, and (3) the nature of the risk being evaluated.[54]

[54] *Environmental Protection Agency: Use of Precautionary Assumptions in Health Risk Assessments and Benefits Estimates* (GAO-01-55, Oct. 16, 2000).

EPA's program offices commonly employ tiered risk assessment approaches that progress from rough screening assessments (for which only limited data may be available) through increasingly detailed and rigorous analyses, if needed. EPA's guidelines and program-specific documents indicate that conservative default assumptions are most often used during initial screening assessments, when the primary task is to determine whether a risk might exist and further analysis is called for. Such screening assessments may use "worst case" assumptions to determine whether, even under those conditions, risk is low enough that a potential problem can be eliminated from further consideration. According to guidelines and related descriptive materials from the program offices, conservative assumptions are used less often in later tiers, as the agency attempts to gather and incorporate more detailed data into its analyses.

Several circumstances may lead to conservative choices playing a less prominent role in EPA risk assessments. For example, the development of more complex and sophisticated models for cancer and noncancer effects places more emphasis on using the full range of available data and characterizing the full range of potential adverse outcomes and effects. Similarly, the increased use of probabilistic analytical methods to derive parameter values will tend to reduce the "compounding" effect of picking conservative point values for each factor. As noted above, the use of tiered risk assessment approaches may also limit the use of default assumptions if more rigorous and case-specific analysis is done beyond initial screening assessments. However, all of these developments may require substantial additional effort and the availability of considerable data, which might not be possible in many cases.

Although not intended to be comprehensive, table 5 illustrates in detail some of the specific assumptions, default data values, or methodological choices that are used in EPA chemical risk assessments. The table concentrates primarily on default choices from EPA's various agencywide risk assessment guidelines. However, to also provide a sense of how default choices are used at the program level, we have included examples of standard assumptions and values employed by two of EPA's program offices. One set of examples illustrates assumptions and choices used by OPP. The second set presents more detailed descriptions of the standard assumptions and choices identified in OW's risk assessment methodology for deriving AWQC for the protection of human health. OW's policy reflects many of the same basic choices that would apply to assessments conducted across the agency, such as the use of uncertainty factors when estimating an RfD.

To the extent that EPA's documents identified for each of these assumptions or choices a reason for its selection, when it would be applied in the risk assessment process, and its likely effect on risk assessment results, we have reported that information. However, it is important to recognize that there is no requirement that agencies provide such information in their guidelines (or even that they have guidelines). In particular with regard to the "likely effects" column, EPA officials cautioned that it is not always appropriate to characterize a single assumption separate from the rest and that it is not always possible to quantify the effect of each default assumption. They noted that, in general, their default assumptions are intended to be public-health protective.

The information presented in table 5 was taken primarily from EPA risk assessment guidelines and related documents but also reflects additional comments provided by EPA officials. (GAO notes and comments appear in parentheses.)

Table 5: EPA Risk Assessment Assumptions and Methodological Choices

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1. Agencywide (ORD) proposed carcinogen risk assessment guidelines			
A carcinogen is a substance or agent that produces or incites cancerous growth. The following items reflect major assumptions or choices identified in the 1999 version of EPA's proposed revision to its 1986 carcinogen risk assessment guidelines.			
1.1 The guidelines use a combination of principles and process to describe a general framework for the application of, or departure from, default assumptions. The proposed guidelines state that the decision to use a default, or not, is a choice considering available information on an underlying scientific process and agent-specific data, depending on which kind of data it is. Generally, • If a gap in basic understanding exists, or if agent-specific data are missing, the default is used without pause. • If data are present, their evaluation may reveal inadequacies that also lead to use of the default. • If data support a plausible alternative to the default, but no more strongly than they support the default, both the default and its alternative are carried through the assessment and characterized by the risk manager. • If the alternative to the default is strongly supported by data, the alternative may be used in place of the default.	(The discussion setting up this framework refers to reports by the National Academy of Sciences' NRC. In particular, the guidelines note that, in 1994, NRC supported continued use of default assumptions as a reasonable way to deal with uncertainty about underlying mechanisms in selecting methods and models for use in risk assessment but also recommended that EPA should consider attempting to give greater formality to its criteria for a departure from default options.) The framework of default assumptions allows risk assessment to proceed when current scientific theory or available case-specific data do not provide firm answers in a particular case.	(General framework outlined for determining whether or not to use default assumptions.)	(Not identified in the proposed guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.2 When cancer effects in exposed humans are attributed to exposure to an exogenous agent, the default assumption is that such data are predictive of cancer in any other exposed human population.	(Not identified in the proposed guidelines, but this is a standard assumption in risk assessment.)	When determining whether the presence or absence of effects observed in a human population is predictive of an agent posing a carcinogenic hazard to other exposed humans.	The guidelines caution that studies either attributing cancer effects in humans to exogenous agents or reporting no effects are often studies of occupationally exposed humans and, therefore, not representative of the general population exposed environmentally to the same agents. Therefore, the guidelines state that this assumption does not err on the side of public-health conservatism, because it could still underestimate the response of certain sensitive human subpopulations.
1.3 When cancer effects are not found in an exposed human population, this information by itself is not generally sufficient to conclude that the agent poses no carcinogenic hazard to this or other populations of potentially exposed humans, including sensitive subpopulations.	Epidemiologic studies usually have low power to detect and attribute responses and typically evaluate cancer potential in a restricted population (e.g., by age, occupation, etc.).	When determining whether the presence or absence of effects observed in a human population is predictive of an agent posing a carcinogenic hazard to other exposed humans.	(Not identified in the proposed guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.4 Positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans. • To demonstrate that a response in animals is not relevant to any human situation, adequate data to assess the relevancy issue must be available.	The assumption is supported by the fact that nearly all of the agents known to cause cancer in humans are carcinogenic in animals in tests with adequate protocols [citations provided]. Moreover, almost one-third of human carcinogens were identified subsequent to animal testing [citations provided]. Further support is provided by research on the molecular biology of cancer processes, which has shown that the mechanisms of control of cell growth and differentiation are remarkably homologous among species and highly conserved in evolution. • (Relevancy issue) There may be instances in which the use of an animal model would identify a hazard in animals that is not truly a hazard in humans [citation provided].	When determining whether the presence or absence of effects observed in an animal population is predictive of an agent posing a carcinogenic hazard to exposed humans, if no adequate human data are present. Available mode of action information is studied for its implications in both hazard and dose-response assessment and its effect on default assumptions.	This assumption is a public-health conservative policy, and it is both appropriate and necessary given that we do not test for carcinogenicity in humans.
1.5 Effects seen at the highest dose tested are appropriate for assessment, but it is necessary that the experimental conditions be scrutinized. • If adequate data demonstrate that the effects are solely the result of excessive toxicity rather than carcinogenicity of the tested agent *per se*, then the effects may be regarded as not appropriate to include in assessment of the potential for human carcinogenicity of the agent.	Animal studies are conducted at high doses in order to provide statistical power, the highest dose being one that is minimally toxic. Consequently, the question often arises whether a carcinogenic effect at the highest dose may be a consequence of cell killing with compensatory cell replication or of general physiological disruption, rather than inherent carcinogenicity of the tested agent. There is little doubt that this may happen in some cases, but skepticism exists among some scientists that it is a pervasive problem [citations provided].	When determining whether the presence or absence of effects observed in an animal population is predictive of an agent posing a carcinogenic hazard to exposed humans, if no adequate human data are present. This is a matter of expert judgment, considering all of the data available about the agent, including effects in other toxicity studies, structure-activity relationships, and effects on growth control and differentiation.	(Not identified in the guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.6 When cancer effects are not found in well-conducted animal cancer studies in two or more appropriate species and other information does not support the carcinogenic potential of the agent, these data provide a basis for concluding that the agent is not likely to possess human carcinogenic potential, in the absence of human data to the contrary.	(Not identified in the guidelines. Instead, the discussion focuses on the limitations of this default assumption. EPA notes, for example, that it is recognized that animal studies and epidemiologic studies have very low power to detect cancer effects and, in some situations, the tested animal species may not be predictive of effects in humans (e.g., arsenic).)	When determining whether the presence or absence of effects observed in an animal population is predictive of an agent posing a carcinogenic hazard to exposed humans, in the absence of human data to the contrary.	The guidelines note that this default assumption about lack of cancer effects has limitations. For example, in some situations, the tested animal species may not be predictive of effects in humans. Therefore, the guidelines discuss the importance of using supplementary data to support conclusions that negative results in animal studies indicate a lack of human hazard.
1.7 Target organ concordance is not a prerequisite for evaluating the implications of animal study results for humans. • An exception to the basic default of not assuming site concordance exists in the context of toxicokinetic modeling. Site concordance is inherently assumed when these models are used to estimate delivered dose in humans based on animal data.	Target organs of carcinogenesis for agents that cause cancer in both animals and humans are most often concordant at one or more sites [citations provided]. However, concordance by site is not uniform.	When determining whether the presence or absence of effects observed in an animal population is predictive of an agent posing a carcinogenic hazard to exposed humans. "It is appropriate under these guidelines to consider the influences of route of exposure, metabolism, and, particularly, hormonal modes of action that may either support or not support target organ concordance between animals and humans. When data allow, these influences are considered in deciding whether the default remains appropriate in individual instances."	This is a public-health conservative science policy.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.8 The default is to include benign tumors observed in animal studies in the assessment of animal tumor incidence if they have the capacity to progress to the malignancies with which they are associated.	This default is consistent with the approach of the National Toxicology Program and the International Agency for Research on Cancer and is somewhat more protective of public health than not including benign tumors in the assessment. This treats the benign and malignant tumors as representative of related responses to the test agent, which is scientifically appropriate [citation provided].	When determining whether the presence or absence of effects observed in an animal population is predictive of an agent posing a carcinogenic hazard to exposed humans. In assessing findings from animal studies, a greater proportion of malignancy is weighed more heavily than a response with a greater proportion of benign tumors.	This is a science policy decision that is somewhat more conservative of public health than not including benign tumors in the assessment.
1.9 Benign tumors that are not observed to progress to malignancy are assessed on a case-by-case basis.	(Not identified in the proposed guidelines.)	When determining whether the presence or absence of effects observed in an animal population is predictive of an agent posing a carcinogenic hazard to exposed humans.	(Not identified in the proposed guidelines.)
1.10 There is a similarity of the basic pathways of metabolism and the occurrence of metabolites in tissues in regard to the species-to-species extrapolation of cancer hazard and risk.	(Not identified in the proposed guidelines.)	When extrapolating from animal studies and considering how metabolic pathways relate across species.	(Not identified in the proposed guidelines.)
1.11 For oral exposure, a human equivalent dose for adults is estimated from data on another species by an adjustment of animal applied oral dose by a scaling factor of body weight to the 0.75 power. • The same factor is used for children.	This adjustment factor is used because it represents scaling of metabolic rate across animals of different sizes. (Also see reason cited under next assumption, and note that an interagency committee recommended this scaling factor as a default approach for federal agencies.) • The same factor is used for children because it is slightly more protective than using children's body weight.	When estimating human equivalent doses in extrapolating from animal studies. Because the factor adjusts for a parameter that can be improved on and brought into more sophisticated toxicokinetic modeling, when such data become available, the default assumption of 0.75 power can be refined or replaced.	(Not identified in the proposed guidelines. However, from other sources, this is generally considered to provide the midpoint of plausible values.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.12 For inhalation exposure, a human-equivalent dose for adults is estimated by default methodologies that provide estimates of lung deposition and of internal dose. • Because of the differences for infants and children, for gases and aerosols, an adjustment is made for their breathing rate and their body weight.	This default assumption, like the one with oral exposure, is selected in part because it lays a foundation for incorporating better data. The use of information to improve dose estimation from applied, to internal, to delivered dose is encouraged, including use of toxicokinetic modeling instead of any default, where data are available. • The guidelines point out that the processes of absorption, distribution, and elimination have important differences among infants and adults [citation provided].	When extrapolating from animal studies and considering how toxicokinetic processes relate across species.	Health conservatism is not an element in choosing the default.
1.13 For a route-to-route exposure extrapolation, the default assumption is that an agent that causes internal tumors by one route of exposure will be carcinogenic by another route if it is absorbed by the second route to give an internal dose.	The rationale is that for internal tumors an internal dose is significant no matter what the route of exposure. Additionally, the metabolism of the agent will be qualitatively the same for an internal dose.	When extrapolating from one route of exposure to another route and considering how toxicokinetic processes relate across species. This is a qualitative assumption. The issue of quantitative extrapolation of the dose-response relationship from one route to another is addressed case by case. Adequate data are necessary to demonstrate that an agent will act differently by one route versus another route of exposure.	This is a qualitative assumption and is considered to be public-health conservative.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.14 If sufficient data are available, a biologically based model for both the observed range and extrapolation below that range may be used. When a biologically based model is not used, • The default procedure for the observed range of data is to use a curve-fitting model for incidence data. • For extrapolation outside of the observed range, the choice of approach is based on the view of mode of action of the agent arrived at in the hazard assessment (covered by items 1.15 through 1.17 below).	While no standard biologically based models are in existence, one may be developed if extensive data exist in a particular case and the purpose of the assessment justifies the investment of resources needed. (See more specific assumptions described below for rationales regarding extrapolation when a biologically based model is not used.)	When assessing the correlation of the observed dose-response relationship to the relationship at lower doses. [Low-dose extrapolation during dose-response assessment.] In the absence of data supporting a biologically based model for extrapolation outside of the observed range, the choice of approach is based on the view of the mode of action of the agent arrived at in the hazard assessment.	(See more specific assumptions described below.)
1.15 When the mode of action information is supportive of linearity or mode of action is not understood, the basic default is to assume linearity and use a linear default approach. The linear approach is to draw a straight line between a point of departure from observed data, generally, as a default, the LED_{10}, and the origin (zero incremental dose, zero incremental response). Other points of departure may be more appropriate for certain data sets; these may be used instead of the LED_{10}.	(Although not mentioned in the proposed guidelines, the assumption of linearity for suspected carcinogens traditionally has been a standard default assumption for EPA.) The LED_{10} is the lower 95-percent limit on a dose that is estimated to cause a 10-percent response. This level is chosen to account (conservatively) for experimental variability. Additionally, it is chosen because it rewards experiments with better designs in regard to number of doses and dose spacing, since these generally will have narrower confidence limits. It is also an appropriate representative of the lower end of the observed range because the limit of detection of studies of tumor effect is about 10 percent.	Low-dose extrapolation during dose-response assessment, in the absence of data supporting a biologically based model.	This approach is generally considered to be public-health conservative. The linear default is thought to generally produce an upper bound on potential risk at low doses. This upper bound is thought to cover the range of human variability although, in some cases, it may not completely do so. EPA considers the linear default to be inherently conservative of public health, without addition of another factor for human variability.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.16 When adequate data on mode of action show that linearity is not plausible, and provide sufficient evidence to support a nonlinear mode of action for the general population and any subpopulations of concern, the default changes to a different approach—a margin of exposure analysis—which assumes that nonlinearity is more reasonable. (A margin of exposure analysis compares the dose at the point of departure with the dose associated with the environmental exposure(s) of interest by computing the ratio between the two.) The departure point is again generally the LED_{10} when incidence data are modeled. When the data available are continuous data, such as blood levels of hormones or organ weight, a NOAEL/LOAEL procedure is typically used.	In the nonlinear approach, the margin that exists between a human exposure of interest and the point of departure is examined for adequacy to protect public health. A margin of exposure analysis may be used as the basis to consider the protectiveness of a possible environmental criterion for regulation or to judge whether an existing exposure might present risk. According to the guidelines, the NOAEL/LOAEL procedures are used with continuous data because modeling approaches for deriving a point of departure from continuous data are not yet available.	Low-dose extrapolation during dose-response assessment, in the absence of data supporting a biologically based model. As noted in the first column, this default is to be used when adequate data on mode of action (1) show that linearity is not plausible and (2) provide sufficient evidence to support a nonlinear mode of action. The guidelines also state that a sufficient basis to support this nonlinear procedure will include data on responses that are key events integral to the carcinogenic process. This means that the point of departure mostly will be from these precursor data rather than tumor incidence data.	(Not identified in the proposed guidelines.)
1.17 When the mode of action information indicates that the dose response may be adequately described by both a linear and a nonlinear approach, then the default is to present both the linear and margin of exposure analyses.	(No additional discussion in the proposed guidelines. See previous assumptions regarding linear and nonlinear approaches.)	Low-dose extrapolation during dose-response assessment, in the absence of data supporting a biologically based model. As noted in the first column, this default is to be used when mode of action information indicates that both a linear and a nonlinear approach may adequately describe the dose response.	(No additional discussion in the proposed guidelines. See previous assumptions regarding linear and nonlinear approaches.)
1.18 A default assumption is made that cumulative dose received over a lifetime, expressed as a lifetime average daily dose, is an appropriate measure of dose (exposure to a carcinogen).	This assumes that a high dose of such an agent over a shorter period of time is equivalent to a low dose spread over a lifetime. This assumption has empirical support [citation provided].	When assessing the correlation of the observed dose-response relationship to the relationship at lower doses. [Low-dose extrapolation during dose-response assessment.]	This is thought to be a relatively public-health conservative assumption.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
2. Agencywide (ORD) guidelines for neurotoxicity risk assessment			
Neurotoxicity is an adverse change in the structure or function of the central and/or peripheral nervous system following exposure to a chemical, physical, or biological agent.			
2.1 It is assumed that an agent that produces detectable adverse neurotoxic effects in experimental animal studies will pose a potential hazard to humans.	This assumption is based on the comparisons of data for known human neurotoxicants [citations provided], which indicate that experimental animal data are frequently predictive of a neurotoxic effect in humans.	When extrapolating data from animal studies to humans. Generally applied in the absence of data on the relevance of effects to potential human risk.	These assumptions are "plausibly conservative" in that they are protective of public health and are also well founded in scientific knowledge about the effects of concern.
2.2 It is assumed that behavioral, neurophysical, neurochemical, and neuroanatomical manifestations are of concern. A biologically significant increase in any of the manifestations is considered indicative of an agent's potential for disrupting the structure or function of the human nervous system.	In the past, the tendency has been to consider only neuropathological changes as endpoints of concern. Based on data on agents that are known human neurotoxicants [citations provided], there is at least one experimental species that mimics the types of effects seen in humans, but in other species tested, the neurotoxic effect may be different or absent.	When extrapolating data from animal studies to humans. Generally applied in the absence of data on the relevance of effects to potential human risk.	(See general statement about these assumptions cited above.)
2.3 It is assumed that the neurotoxic effects seen in animal studies may not always be the same as those produced in humans. Therefore, it may be difficult to determine the most appropriate species in terms of predicting specific effects in humans.	The fact that every species may not react in the same way is probably due to species-specific differences in maturation of the nervous system, differences in timing of exposure, metabolism, or mechanisms of action.	When extrapolating data from animal studies to humans. Generally applied in the absence of data on the relevance of effects to potential human risk.	(See general statement about these assumptions cited above.)
2.4 It is also assumed that, in the absence of data to the contrary, the most sensitive species is used to estimate human risk.	This is based on the assumption that humans are as sensitive as the most sensitive animal species tested. This provides a conservative estimate of sensitivity for added protection to the public.	When extrapolating data from animal studies to humans. Generally applied in the absence of data on the relevance of effects to potential human risk.	Provides a conservative estimate of sensitivity. (Also see general statement about these assumptions cited above.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
2.5 As with other noncancer endpoints, it is assumed that there is a nonlinear dose-response relationship for neurotoxicants.	Although there may be a threshold for neurotoxic effects, these are often difficult to determine empirically. Therefore, a nonlinear relationship is assumed to exist for neurotoxicants.	When extrapolating data from animal studies to humans. Generally applied in the absence of data on the relevance of effects to potential human risk.	(See general statement about these assumptions cited above.)
3. Agencywide (ORD) guidelines for reproductive toxicity risk assessment Reproductive toxicity focuses on toxic effects regarding the male and female reproductive systems, including outcomes of pregnancy and lactation.			
3.1 An agent that produces an adverse reproductive effect in experimental animals is assumed to pose a potential threat to humans.	This assumption is based on comparisons of data for agents that are known to cause human reproductive toxicity [citations provided]. In general, the experimental animal data indicated adverse reproductive effects that are also seen in humans.	When extrapolating data from experimental animal studies to humans, in the absence of adequate human data	(Not identified in the guidelines.)
3.2 Effects of xenobiotics on male and female reproductive process are assumed generally to be similar unless demonstrated otherwise. For developmental outcomes, the specific effects in humans are not necessarily the same as those seen in the experimental species. However, adverse developmental outcomes in laboratory mammalian studies are presumed to predict a hazard for adverse developmental outcome in humans.	Because similar mechanisms can be identified in the male and female of many mammalian species, effects of xenobiotics on male and female reproductive processes are assumed generally to be similar across species, unless demonstrated otherwise. The assumption for developmental outcomes is made because of the possibility of species-specific differences in timing of exposure relative to critical periods of development, pharmacokinetics (including metabolism), developmental patterns, placentation, or modes of action.	When extrapolating data from experimental animal studies to humans, in the absence of adequate human data.	(Not identified in the guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
3.3 In the absence of information to determine the most appropriate experimental species, data from the most sensitive species should be used.	It is assumed that the most sensitive species is most appropriate because, for a majority of agents known to cause human reproductive toxicity, humans appear to be as or more sensitive than the most sensitive animal species tested, based on data from studies that determined dose on a body weight or air concentration basis [citations provided].	When extrapolating data from experimental animal studies to humans, in the absence of adequate human data, and in the absence of sufficient information (e.g., pharmacokinetic data) to determine the most appropriate experimental species.	(Not identified in the guidelines.)
3.4 In the absence of information to the contrary, an agent that affects reproductive function in one sex is assumed to adversely affect reproductive function in the other sex.	This assumption for reproductive risk assessment is based on three considerations: 1. For most agents, the nature of the testing and data available are limited, reducing confidence that the potential for toxicity to both sexes and their offspring has been examined equally. 2. Exposures of either males or females have resulted in developmental toxicity. 3. Many of the mechanisms controlling important aspects of reproductive system function are similar in females and males, and therefore could be susceptible to the same agents.	When extrapolating data from experimental animal studies to humans, in the absence of adequate human data. In the absence of information to the contrary.	(Not identified in the guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
3.5 A nonlinear dose-response curve is assumed for reproductive toxicity.	This is based on known homeostatic, compensatory, or adaptive mechanisms that must be overcome before a toxic endpoint is manifested and on the rationale that cells and organs of the reproductive system and the developing organism are known to have some capacity for repair of damage. Although a threshold may exist for endpoints of reproductive toxicity, it usually is not feasible to distinguish empirically between a true threshold and a nonlinear low-dose relationship.	When extrapolating data from experimental animal studies to humans, in the absence of adequate human data. In a quantitative dose-response analysis, mode of action, pharmacokinetic, and pharmacodynamic information should be used to predict the shape of the dose-response curve when sufficient information of that nature is available. When that information is insufficient, it has generally been assumed that there is a nonlinear dose response for reproductive toxicity.	(Not identified in the guidelines.)

4. Agencywide (ORD) guidelines for developmental toxicity risk assessment

Developmental toxicity risk assessment focuses on risk to human development, growth, survival, and function because of exposure to environmental agents prior to conception, prenatally, or to infants and children.

4.1 It is assumed that an agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans following sufficient exposure during development.	This assumption is based on the comparisons of data for agents known to cause human developmental toxicity [citations provided] which indicate that, in almost all cases, experimental animal data are predictive of a developmental effect in humans.	When extrapolating data from animal studies to humans for hazard identification/dose-response analysis. Generally applied in the absence of adequate human data.	(Not identified in the guidelines.)
4.2 It is assumed that all of the four manifestations of developmental toxicity (death, structural abnormalities, growth alternations, and functional deficits) are of concern. A biologically significant increase in any of the four manifestations is considered indicative of an agent's potential for disrupting development and producing a developmental hazard.	In the past, there has been a tendency to consider only malformations or malformations and death as endpoints of concern. From data on agents that are known to cause human developmental toxicity [citations provided], there is usually at least one experimental species that mimics the types of effects seen in humans, but in other species tested, the type of developmental perturbation may be different.	When extrapolating data from animal studies to humans for hazard identification/dose-response analysis. Generally applied in the absence of adequate human data.	(Not identified in the guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
4.3 It is assumed that the types of developmental effects seen in animal studies are not necessarily the same as those that may be produced in humans.	This assumption is made because it is impossible to determine which will be the most appropriate species in predicting the specific types of effects seen in humans. The fact that every species may not react the same way could be due to species-specific differences in critical periods, differences in timing of exposure, metabolism, developmental patterns, placentation, or mechanisms of action.	When extrapolating data from animal studies to humans for hazard identification/dose-response analysis. Generally applied in the absence of adequate human data.	(Not identified in the guidelines.)
4.4 The most appropriate species is used to estimate human risk when data are available (e.g., pharmacokinetics). In the absence of such data, it is assumed that the most sensitive species is appropriate for use.	This assumption is based on observations that humans are as sensitive or more so than the most sensitive animal species tested for the majority of agents known to cause human developmental toxicity [citations provided].	When extrapolating data from animal studies to humans for hazard identification/dose-response analysis. Generally applied in the absence of adequate human data.	(Not identified in the guidelines.)
4.5 In general, a threshold is assumed for the dose-response curve for agents that produce developmental toxicity.	This is based on the known capacity of the developing organism to compensate for or to repair a certain amount of damage at the cellular, tissue, or organ level. In addition, because of the multipotency of cells at certain stages of development, multiple insults at the molecular or cellular level may be required to produce an effect on the whole organism.	When evaluating the dose-response relationship.	(Not identified in the guidelines.)
4.6 For developmental toxic effects, a primary assumption is that a single exposure at a critical time in development may produce an adverse developmental effect, i.e., repeated exposure is not a necessary prerequisite for developmental toxicity to be manifested.	(Not identified in the guidelines.)	When doing dose-response evaluation.	(Not identified in the guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
4.7 If absorption [of the administered dose of an agent] in the experimental species has been determined, but human absorption is not known, human absorption is generally assumed to be the same as that for the species with the greatest degree of absorption.	(Not identified in the guidelines, but this assumption is a variation on the inference assumption identified under item 4.4, and other related EPA guidelines are referenced as well.)	When doing dose-response evaluation using data from animal studies.	(Not identified in the guidelines.)
4.8 When determining the reference dose or reference concentration for developmental toxicity: • The most sensitive developmental effect from the most appropriate and/or sensitive mammalian species is used for determining the NOAEL, LOAEL, or benchmark dose. • Uncertainty factors for developmental and maternal toxicity generally include a 10-fold factor for interspecies variation and a 10-fold factor for intraspecies variation. Additional factors may be applied to account for other uncertainties or additional information that may exist in the database. In general, an uncertainty factor is not applied to account for duration of exposure.	(Not identified in the section on RfD and RfC, but the assumptions regarding use of the most sensitive effect and most appropriate and/or sensitive species are variations on inference assumptions described above.)	When determining the reference dose or concentration for developmental toxicity (the RfD_{DT} or RfC_{DT}) –a level at or below which it is assumed that no significant risk occurs.	(Not identified in the guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
5. Agencywide (ORD) guidelines for health risk assessment of chemical mixtures (1999 draft of supplemental guidance)			
5.1 For the component chemicals that show similar toxicity, dose addition is recommended. (When the effect of the combination is the effect expected from the equivalent dose of an index chemical, the equivalent dose is the sum of the component doses scaled by their potency relative to the index chemical. This sum of the exposure levels is a weighted sum.) Dose addition is different from response addition because two assumptions are made: that all of the components have similar uptake, pharmacokinetics, and toxicologic processes, and that the (log probit) dose-response curves of the components are parallel.	Several studies have demonstrated that dose (or concentration) addition often predicts reasonably well the toxicities of mixtures composed of a substantial variety of both similar and dissimilar compounds (citations provided). The assessment of multiple toxicant exposure has been addressed by the American Conference of Governmental Industrial Hygienists, OSHA, the World Health Organization, and the NRC (citations provided). Although the focus and purpose of each group was somewhat different, all of the recommended approaches included some type of dose-additive model.	Used in dose-response assessment. Dose addition is the default approach in situations where the dose for each individual component is at a level at which effects are not expected to occur, be observable, or be of concern. However, when the doses are combined, effects of concern are then expected or observed in response to the higher dose level of the mixture.)	(Not identified in the guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
5.2 For the component chemicals in a mixture that show dissimilar toxicity, response addition is recommended. (Under response addition, the general procedure is to first determine the risks per exposure for the individual components; the mixtures risk is then estimated by adding the individual risks together.) Response addition is different from dose addition in that it does not assume similar kinetics or a similar mode of action and does not assume parallel dose-response curves. It assumes that the components of the mixture are considered to be functionally independent of one another at low-exposure levels, so that the risks may be added together. (This sum of the effects of the individual chemicals is a conditional sum.)	Dose-additive models may not be the most biologically plausible approach if the compounds do not have the same mode of toxicologic action.	Used in dose-response assessment. Response addition is the default approach when the component chemicals are functionally independent. It is most often applied when an effect that is of concern is expected to be present at low-dose levels for each of the component chemicals, even though it is highly unlikely to be observable at these low levels in either epidemiologic or toxicologic studies. Because response addition does not require a similar mode of action across the chemicals in the mixture, it allows for combining risks across different types of endpoints.	(Not identified in the guidelines.)
5.3 If interactions data are available, the default recommendation is that they be incorporated into the risk assessment either by using the interactions based hazard index or by including a qualitative assessment of the direction and magnitude of the impact of the interaction data.	(Not identified in the guidelines.)	Used in dose-response assessment.	(Not identified in the guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
6. Agencywide (ORD) guidelines for ecological risk assessment			
These guidelines focus on exposures to one or more anthropogenic chemical, physical, or biological stressors that may result in adverse ecological effects. In comparison to the NAS risk paradigm, the information here reflects the novel approaches and methodological choices advocated by EPA in ecological risk assessments. Only a subset of the primary methodological choices are presented—rather than specific default assumptions, reflecting the level of specificity in EPA's ecological risk assessment guidance document.			
6.1 EPA advocates tiering ecological risk assessments such that conservative approaches are first employed in both data and model use, followed by a more detailed assessment process (if warranted). When a risk has been identified, subsequent tiers use additional data to address the uncertainties of the initial assessment(s). Examples of methodological choices in first tier of a ecological risk assessment: • use simple rather than complex models; • analyze uncertainty propagation and how uncertainty in individual parameters can affect the overall uncertainty in the results (e.g., calculate error bounds on a point estimate); and • conduct tests designed to evaluate effects such as lethality and immobility.	Allows determinations regarding how extensive a risk assessment should be, taking into consideration risk management goals. The underlying assumptions and the risk scenarios can be carried through to risk characterization phase in a first-tier risk assessment, allowing their plausibility to be discussed and reevaluated.	Applied in most ecological risk assessments.	Precautionary approach maintaining a higher degree of conservatism in the risk assessment.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
6.2 Methodological choices regarding data issues: • When existing data are few and new data cannot be collected, consider extrapolation from existing data when characterizing effects of stressors on assessment endpoints. • Employ field-observational studies that represent exposures and effects better than estimates generated from laboratory studies or theoretical models. • Use statistical tests (e.g., correlation, clustering, factor analysis) or indices to measure and evaluate effects. • Directly measure environmental media (or a combination of modeling and direct measurement) if stressors have already been released into the environment, if possible. • Use point estimate/descriptor approach when there is not enough information to describe a distribution.	Better characterization of stressor-assessment endpoint relationships and better ability to accurately formulate and address risk hypotheses: • Extrapolation of data collected from other locations or on organisms where similar circumstances exist can be a useful proxy—particularly when obtaining original data is unachievable. • Field-observational studies (surveys) are necessary to measure biological changes in uncontrolled situations that best mimic the relationship between assessment endpoint and stressor [citations provided]. • Large-scale ecological processes are difficult to detect in laboratory settings.	General data considerations during early first- and subsequent-tier risk assessment stages of problem formulation phase—particularly when data or relationships cannot be defined in a traditional laboratory setting or where assessments of multiple stressors or site-specific factors significantly influence exposure. Studies that minimize the amount of extrapolation are preferred.	Data choice(s) can effect a risk assessment in a variety of ways, for example: • More accurate conclusions in laboratory settings may be possible; however, laboratory controls may limit the range of responses and/or may not reflect responses in the environment. • Results can be presented as a series of point estimates with different aspects of uncertainty reflected in each (e.g., classical statistical methods such as confidence limits, or percentiles, can be employed).

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
6.3 Generally, potential dose of a chemical is quantified as the amount of chemical ingested, inhaled, and/or applied dermally. Specifically, potential average daily dose for ingested media is a function of: • average contaminant concentration in the type of food (using modeled or measured values); • fraction of intake of the food type that is from the contaminated area; • normalized ingestion rate of the food type on a wet-weight basis; • number of contaminated food types.	Allows for the establishment of a standardized approach in deriving values of exposure for ingested media (food or soil).	Determination of dose in analysis phase.	(Not indicated in guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
6.4 In creating an exposure profile, estimates of exposure should be considered, at a minimum, along three dimensions: intensity, time, and space. These, and other exposure guidelines, are outlined below: • Intensity may be expressed as the amount of chemical contacted per day or the number of pathogenic organisms per unit area. • The temporal dimension of exposure is best addressed with the parameters of duration, frequency, and timing. • In its simplest form, a stressor is quantified as a concentration, with the assumption that the chemical is well mixed or that the organism moves randomly through the medium. • "High end" exposure should refer to estimates that are expected to fall between the 90th and 99.9th percentile of the exposure distribution. • Bounding estimates should refer to those higher than any actual exposure.	EPA advocates such methodological choices regarding exposure profiles in order to allow a risk assessor to best estimate risks. The exposure profile, in turn, is combined with an effects profile to estimate risks.	Production of a summary exposure profile during analysis phase that: • identifies the receptor (i.e., the exposed ecological entity); • describes the course a stressor takes from the source to the receptor (i.e., the exposure pathway); and • describes the intensity and spatial and temporal extent of co-occurrence or contact.	(Not indicated in guidelines.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
6.5 When sufficient data are available to quantify exposure and effects estimates, the simplest approach for comparing the estimates is a ratio (or quotient). A quotient addition approach assumes that toxicities are additive or approximately additive (this assumption may be mostly applicable when the modes of action of chemicals in a mixture are similar).	Quotient method is commonly used for chemical stressors, where reference or benchmark toxicity values are widely available. Principal reasons for selecting quotient method: • It is simple and quick to use and risk assessors and managers are familiar with its application. • It provides an efficient, inexpensive means of identifying high- or low-risk situations that can allow risk management decisions to be made without the need for further information. • Quotients can be used to integrate risks of multiple chemical stressors.	When performing activities of risk characterization phase (i.e., risk estimation, risk description, reporting risk).	(Not indicated in guidelines.)

The following sections illustrate the types of additional, program-specific assumptions and choices identified by individual program offices within EPA. We only provide examples from two of EPA's offices—the Office of Pesticide Programs and the Office of Water. However, other offices can also have their own preferences with regard to risk assessment assumptions and methods tied to the particular exposures of concern to their programs.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
7. Office of Pesticide Programs science policy papers and guidance documents regarding risk assessments for pesticides			
OPP has published an expanding series of over 20 science policy papers—many still at the draft stage—on various issues related to regulation of pesticides in response to the Food Quality Protection Act of 1996. The following rows illustrate some of the major assumptions or choices described within those science policy papers or guidance documents.			
7.1 Applying the FQPA tenfold safety factor The FQPA requires EPA to apply, in the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children. The Administrator of EPA may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such a margin will be safe for infants and children. Where reliable data are available, OPP favors an approach that attempts to make a specific case-by-case determination as to the size of the additional factor rather than rely on the tenfold default value.	Statutory provision of the FQPA, in section 408(b)(2)(C). (In draft policy papers on this subject, EPA cited a number of reasons regarding the agency's preference for making a case-by-case determination of an appropriate safety factor. The agency pointed out, in particular, that because OPP's approach to estimating exposure in the absence of extensive, specific data is typically very conservative, OPP can usually conclude, with a high degree of confidence, that its approach adequately protects infants and children. EPA is also revising its toxicology and exposure data requirements in response to the FQPA.)	(This is primarily a "risk management" issue when EPA is "establishing, modifying, leaving in effect, or revoking a tolerance or exemption for a pesticide chemical residue." However, it affects risk assessment by OPP in that it calls for a determination of whether the available data are reliable and a different "margin of safety" will be safe for infants and children.)	(The intent of this additional "safety factor" is precautionary—to give special consideration with respect to exposure and toxicity to infants and children.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
7.2 Dietary exposure estimates (draft): For regulatory purposes, acute and chronic dietary exposure to pesticides in foods are estimated using indirect modeling approaches that consider pesticide residues in food and the amount of food consumed. EPA assesses dietary exposure using a tiered approach, proceeding from conservative to more refined assumptions and varying by acute (short-term) and chronic (long-term) assessments. Initially, EPA uses deterministic assessments based on various assumptions about the concentration of pesticide residue in the food. For more refined dietary assessments, EPA uses probabilistic exposure assessments. (See details for these various tiers in rows 7.2.1 through 7.2.4 below.]	The tiered approach is used to conserve limited resources.	When assessing dietary exposures to pesticides. Analysis proceeds through more rigorous tiers, as the overall risk assessment situation requires, when data exist.	(EPA characterizes the initial tiers, especially tier 1, as producing conservative exposure estimates. The higher level tiers are characterized as producing more accurate, and less conservative, exposure assessments.)
7.2.1 Tier 1 approach to estimating dietary risk from pesticides in foods (draft): • Both acute and chronic assessments use deterministic values (point estimates) for exposure, assuming residues on foods to be at maximum legal tolerance levels and that 100 percent of the crop is treated with the pesticide.	The tiered approach is used to conserve limited resources.	When assessing dietary exposures to pesticides. Analysis proceeds through more rigorous tiers, as the overall risk assessment situation requires, when data exist.	Tolerance levels for residues used in Tier 1 dietary exposure estimates are not expected to accurately reflect actual residues in ready-to-eat foods; rather, they are intended to provide inputs for “worst-case” exposure estimates. Residue data for Tier 1 assessments meet the criterion for conservative exposure factors.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
7.2.2 Tier 2 approach to estimating dietary risk from pesticides in foods (draft): • Acute assessments use deterministic values for exposure and assume that residues on single-serving size items are at maximum legal tolerance levels, residues for blended commodities are based on average residue from field trials or monitoring data, and 100 percent of the crop is treated with the pesticide. • Chronic assessments use deterministic values and assume residues are at tolerance levels, but use actual percentage of the crop treated.	The tiered approach is used to conserve limited resources.	When assessing dietary exposures to pesticides. Analysis proceeds through more rigorous tiers, as the overall risk assessment situation requires, when data exist.	Assessments are refined in Tier 2 using more realistic values for pesticide residues. (In its guidance for performing aggregate exposure assessments, OPP noted that field trial data, which are traditionally the primary source of residue data in foods, overestimate the residues that are likely to occur in foods as actually consumed. According to the agency, this is because they reflect the maximum application rate and shortest pre-harvest interval, and represent residue levels “at the farm gate.” OPP pointed out that data more reflective of residues on foods as consumed are often available from monitoring data in which food samples are obtained closer to the dinner table in the chain of commerce and analyzed.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
7.2.3 Tier 3 approach to estimating dietary risk from pesticides in foods (draft): • Acute assessments use probabilistic values (distributional estimates), an empirical distribution frequency from field trials for single-serving items, average residue data from field trials or monitoring data for blended commodities, and actual percentage of the crop treated. These assessments also consider food processing factors. • Chronic assessments use deterministic values, average residue data from field trials or monitoring data for both blended and single-serving commodities, and actual percentage of the crop treated. Again, food processing factors are considered.	The tiered approach is used to conserve limited resources.	When assessing dietary exposures to pesticides. Analysis proceeds through more rigorous tiers, as the overall risk assessment situation requires, when data exist.	In Tiers 3 and 4, pesticide residue data are combined with assumptions on actual pesticide application rates, stability, etc., to refine further residue estimates in foods as they are consumed. (See note on field trial and monitoring data in row 7.2.2 above.)
7.2.4 Tier 4 approach to estimating dietary risk from pesticides in foods (draft): • Acute assessments use probabilistic values, market basket survey data on consumption, actual percentage of the crop treated, and consider cooking, residue decline, residue degradation, and other factors that may affect residues in foods as they are consumed. • Chronic assessments use the same types of data as acute assessments, but with deterministic values.	The tiered approach is used to conserve limited resources.	When assessing dietary exposures to pesticides. Analysis proceeds through more rigorous tiers, as the overall risk assessment situation requires, when data exist.	In Tiers 3 and 4, pesticide residue data are combined with assumptions on actual pesticide application rates, stability, etc., to refine further residue estimates in foods as they are consumed.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
7.3 Assessing Residential Exposures EPA notes that although its residential exposure assessments "are designed to be as realistic as possible," the assessments also are "generally conservative." Specific assumptions include: a. Assume high amounts of pesticide residues will transfer to a person. (EPA generally assumes 20-50 percent of the residues will transfer.) b. Assume no residue dissipation. In other words, all the residues available initially are available throughout the time a person is exposed. c. Assume that a person has no clothing on to protect from exposure. d. Assume 2 to 8 hours of continuous contact. (Note that EPA was reviewing and considering whether to update some of the detailed exposure scenario assumptions in its standard operating procedures (SOPs) for residential assessments.)	This conservatism adds an extra measure of safety when regulating pesticides. Explanations for the specific assumptions include: a. The highest reasonably possible transfer rate must be assumed for safety. b. Dissipation rate is based on many factors (heat, sunlight, and rain, etc.) so EPA says it must include the conservative prospect that in a given case there is no residue dissipation. c. Assumed because little or no clothing is a possible realistic scenario in some circumstances. d. (No additional explanation provided.)	When assessing risks associated with residential exposures to (residential uses of) pesticides.	EPA said that when scientists have studied people in the real world (including the children of farmworkers) they have generally found a person's exposure to be less than that predicted by EPA's exposure assessments. (In other guidance documents, EPA points out that its residential SOPs are by nature designed to produce screening-level assessments that are intentionally conservative in nature.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
7.4 Guidance for Performing Aggregate Exposure and Risk Assessment Aggregate exposure and risk assessment involves the analysis of a single chemical exposure by multiple pathways of exposure (i.e., food, drinking water, and residential, nonoccupational), and all relevant routes of exposure (i.e., oral, dermal, and inhalation). EPA's revised guidelines support an approach in which an analyst assesses exposure on an individual-by-individual basis, culminating in a representative population of interest. This approach differs from EPA's interim guidelines. (According to the interim guidelines, aggregate assessments most frequently added the "high-end" or upper-bound point estimates from the drinking water and residential exposure pathways to a point on the distribution of food ingestion exposure, e.g., the 99.9th percentile.) Aggregate exposure and risk assessments will be more realistic to the extent that the appropriate temporal, spatial, and demographic factors that affect exposure to an individual are understood and accounted for. When these data are not available, reasonable assumptions that do not underestimate exposure can be used. Once an aggregate exposure and risk assessment is completed for one individual and repeated for many individuals, population and subpopulation distributions of total exposures and risk may be constructed by probabilistic techniques. Distributional data analysis is preferred.	(EPA revised its approach to aggregate exposure and risk assessment in response to the FQPA's requirement that the agency consider aggregate exposure in its decision making.) EPA noted in the guidance that aggregate exposure assessments built individual by individual, culminating in a total exposure to the population, may allow for probabilistic treatment of data incorporating all pathways of exposure, (i.e., food, drinking water, and residential). Distributional data analysis is preferred as this tool allows an aggregate exposure assessor to more fully understand the uncertainty and variability inherent in the data set.	When performing aggregate exposure and risk assessments	(Not directly addressed in the general discussion in the revised guidance. The inference from EPA's comparison to the interim guidance is that the revised practices should result in less conservative estimates than the interim practices. However, the revised guidance also emphasizes the use of "reasonable assumptions that do not underestimate exposure" when data are not available, so there still may be a precautionary element.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
8. Office of Water Risk Assessments			
OW has published a collection of guidance documents relating to water quality issues, based primarily on mandates derived from the Clean Water Act (CWA) and Safe Drinking Water Act (SDWA). For illustrative purposes, emphasis here is on assumptions and methodological choices taken from *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health, EPA-822-B-00-005 (October 2000)*. This document provides detailed guidance on developing Ambient Water Quality Criteria (AWQC), with organized procedures for evaluating cancer risk, noncancer health effects, human exposure, and bioaccumulation potential in fish. In this guidance, EPA states that protective assumptions are made regarding potential human exposure intakes at an appropriate level of conservatism where uncertainties exist. Furthermore, criteria are derived to be protective, not predictive, of an exact percentile of the total population that is protected.			
8.1 EPA has identified a number of standard or default exposure factors: • All drinking water consumed is contaminated at the criteria level. • All fish consumed is contaminated at the criteria level and all fish may come from one water body. • Body weight of a child ages 1 to 3 is 13 kg (when the age group is ages 1 to 14, body weight is 30 kg). • Body weight of an adult is 70 kg. • Body weight of a woman of childbearing age is 67 kg. • Daily untreated surface water consumed is 2 liters. • Daily fish consumption is 17.5 g for general adult population and (average) sport fishers; 142.4 g for subsistence fishers. • Criteria generally represent ambient pollutant concentrations that are acceptable based on a lifetime (70 years) of exposure.	Body weight, water intake, and fish intake are default parameters specific to target populations that are considered important when determining AWQC values. Drinking water and fish intake values are 90th percentile estimates, based on most recent USDA survey data reflecting the 90th percentile of the general population (1994-96 CSFII data), and are percentiles selected to ensure protection of the majority of consumers of drinking water and fish.	Used in the derivation of AWQC, and also, to be consistent with Section 101(a) of CWA which specifies possible water body uses (e.g., consumption of fish).	Conservative assumptions in choosing exposure parameters support the goal of protecting the majority of the population.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
8.2 In setting RfDs for noncarcinogens, EPA advocates the use of uncertainty factors and, if needed, a modifying factor to account for areas of scientific uncertainty in toxicity databases. EPA recommends a default of 10 for uncertainty factors and a default of 1 for modifying factors when lacking other information. Specifically, EPA recommends applying a 1-, 3-, or 10-fold uncertainty factor when: a. extrapolating from valid data in studies using long-term exposure to average healthy humans; b. extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or inadequate; c. extrapolating from less-than-chronic results on experimental animals when there are no useful long-term human data; or d. deriving an RfD from an "incomplete" database. EPA recommends a 3- or 10-fold uncertainty factor when: e. deriving an RfD from a LOAEL, instead of a NOAEL. EPA advocates using professional judgment in determining the modifying factor, the magnitude of which is greater than zero and less than or equal to 10, being dependent on assessment of uncertainties of relevant studies and databases.	Uncertainty factors listed in the previous column are used to more accurately determine an RfD by more closely identifying and incorporating, respectively: a. interhuman variability (to account for variation in sensitivity among the members of the human population); b. experimental animal-to-human extrapolation (interspecies variation); c. subchronic to chronic extrapolation (to account for uncertainty in extrapolating from less-than-chronic NOAELs or LOAELs to chronic NOAELs); d. database completeness (to account for the inability of any single study to adequately address all possible adverse outcomes); and e. LOAEL-to-NOAEL extrapolation. A modifying factor is to be used when the areas of scientific uncertainty addressed with uncertainty factors do not represent all of the uncertainties in the estimation of a RfD.	Deriving water quality criteria for the protection of human health from noncancer effects (i.e., noncarcinogenic chemicals) via the determination RfDs. Specifically, the RfD is used with additional information regarding exposure and the bioaccumulation potential of the substance to derive an AWQC for noncancer effects. According to EPA, the "[c]hoice of appropriate uncertainty factors and modifying factors must be a case-by-case judgment by experts and should account for each of the applicable areas for uncertainty and nuances in the available data that impact uncertainty."	Conservative approach resulting in lower RfD values.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
8.3 EPA identified both 10^{-6} and 10^{-5} as appropriate cancer target risk levels, and said that highly exposed populations should not exceed a 10^{-4} cancer risk level. Cancer risk level of 10^{-6} is based on a fish intake rate of 17.5 g/day for general population and sport anglers, a fish intake rate of 142.4 g/day for subsistence fishers, and a drinking water intake rate of 2 liters per day for each of these groups.	Such values reflect appropriate target risk levels for health protection of the general population. The cancer risk levels increase the degree of consistency between the drinking water program, ambient water program, and other EPA programs.	(None given.)	(None given.)
8.4 Under some circumstances, it may be appropriate to use a point within an RfD range as the basis for deriving AWQC, rather than the single point default estimate of the RfD, when the uncertainty factor is 100 or greater and the range is either a quarter or half log unit to either side of the calculated RfD.	This methodological choice offers some flexibility for site-specific or contaminant-specific situations but remains protective of public health.	Where either new risk assessment studies or site-specific information support derivation of an AWQC from a point within RfD range.	AWQC may increase or decrease.
8.5 Consideration of nonwater sources of exposure (e.g., ingestion and/or inhalation exposure) is recommended when determining a relative source contribution (RSC) factor to apply to a nonlinear carcinogen point-of-departure (POD) or a RfD. Apply an estimate of the RSC factor (between 20 and 80 percent) to the RfD when adequate exposure data do not exist, using an exposure decision tree approach.	In deriving RfD, use of RSC allows for assessing total human exposure to a contaminant and apportions the RfD among the media of concern. • Use of “Exposure Decision Tree” approach allows for use of either subtraction or percentage methods, depending on chemical circumstances, within the 20- to 80- percent range.	Derivation or revision of an AWQC based on RfDs or nonlinear carcinogen PODs.	Conservative and protective approach when known or anticipated nonwater sources of exposure are anticipated.

(Continued From Previous Page)

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
8.6 EPA recommends using a bioaccumulation factor (BAF) rather than a bioconcentration factor as previously set forth in the 1980 Methodology.	This change was made in order to reflect the uptake of a contaminant by aquatic organisms from all sources (e.g., water, food, sediment) rather than just from the water column.	BAF values are used in calculations of AWQC for carcinogens (in both linear and nonlinear approaches) and for noncarcinogens.	The ambient water quality criteria for highly bioaccumulative pollutants may be up to 2 orders of magnitude lower than criteria derived with bioconcentraton factors.

Source: Compiled from GAO review of EPA risk assessment guidelines and related documents and from additional comments provided by agency officials.

Risk Characterization

As with exposure assessment, the program offices typically are responsible for completing the risk characterization. EPA does, however, have several documents that provide agencywide guidance on how such characterization is to be done. The guidance includes a February 26, 1992, memorandum from the EPA Deputy Administrator entitled, "Guidance on Risk Characterization for Risk Managers and Risk Assessors," and a March 21, 1995, document issued by the EPA Administrator entitled, "Policy for Risk Characterization at the U.S. Environmental Protection Agency." EPA also has developed a *Risk Characterization Handbook* to provide more detailed guidance to agency staff.

In the statement accompanying its 1994 report *Science and Judgment in Risk Assessment*, NRC said that although EPA's overall approach for assessing risks was fundamentally sound, the agency "must more clearly establish the scientific and policy basis for risk estimates and better describe the uncertainties in its estimates of risk." In March 1995, the EPA Administrator issued the agency's risk characterization policy and guidance, which reaffirmed the principles and guidance in the agency's 1992 policy. EPA's guidance document defined risk characterization as the final step in the risk assessment process that (1) integrates the individual characterizations from the hazard identification, dose-response, and exposure assessments; (2) provides an evaluation of the overall quality of the assessment and the degree of confidence the authors have in the estimates of risk and conclusions drawn; (3) describes the risks to individuals and populations in terms of extent and severity of probable harm; and (4) communicates the results of the risk assessment to the risk

manager. Discussing "guiding principles" for risk characterization, EPA emphasized that the integration of information from the three earlier stages of risk assessment, discussion of uncertainty and variability, and presentation of information to risk managers requires the use of both qualitative and quantitative information. For example, when assumptions are made in exposure assessment, EPA said that the source and general logic used to develop the assumptions should be described, as well as the confidence in the assumptions made and the relative likelihood of different exposure scenarios.

In the 1995 policy statement, EPA said that risks should be characterized in a manner that is clear, transparent, reasonable, and consistent with other risk characterizations of similar scope. EPA said that all assessments "should identify and discuss all the major issues associated with determining the nature and extent of the risk and provide commentary on any constraints limiting fuller exposition." The policy also said risk characterization should (1) bridge the gap between risk assessment and risk management decisions; (2) discuss confidence and uncertainties involving scientific concepts, data, and methods; and (3) present several types of risk information (i.e., a range of exposures and multiple risk descriptors such as high ends and central tendencies). The policy stated that each risk assessment used in support of decision making at EPA should include a risk characterization that follows the principles and reflects the values outlined in the policy. However, the policy statement went on to say that it and the associated guidance did not establish or affect legal rights or obligations.

Some of EPA's other risk assessment guidelines also discuss and recommend certain approaches to the risk characterization phase. For example, EPA's proposed guidelines for carcinogen risk assessment call for greater emphasis on the preparation of "technical" characterizations to summarize the findings of the hazard identification, dose-response assessment, and exposure assessment steps. The agency's risk assessors are then to use these technical characterizations to develop an integrative analysis of the whole risk case. That integrative analysis is in turn used to prepare a less extensive and nontechnical Risk Characterization Summary intended to inform the risk manager and other interested readers. EPA identified several reasons for individually characterizing the results of each analysis phase before preparing the final integrative summary. One is that the analytical assessments are often done by different people than those who do the integrative analysis. The second is that there is very often a lapse of time between the conduct of hazard and dose-response analyses

and the conduct of the exposure assessment and integrative analysis. Thus, according to EPA, it is necessary to capture characterizations of assessments as the assessments are done to avoid the need to go back and reconstruct them. Finally, several programs frequently use a single hazard assessment for different exposure scenarios. The guidelines also point out that the objective of risk characterization is to call out any significant issues that arose within the particular assessment being characterized and inform the reader about significant uncertainties that affect conclusions, rather than to recount generic issues that are covered in agency guidance documents.

In another example, EPA's ecological risk guidelines emphasize that risk characterization is a means for clarifying relationships between stressors, adverse effects, and ecological entities. In addition, this phase of the risk assessment process is a time to reach conclusions regarding the occurrence of exposure(s) and the adversity of existing or anticipated effects. Specifically, EPA guidance describes three ecological risk characterization activities: (1) risk estimation (i.e., integrating exposure and effects data and evaluating uncertainties); (2) risk description (i.e., interpreting and discussing available information about risks to the assessment endpoints); and (3) risk reporting (i.e., estimating risks indicating the overall degree of confidence in such estimates, citing lines of evidence to support risk estimates, and addressing assumptions and uncertainties). Similar to EPA-wide guidance on risk characterization, EPA's ecological risk characterization guidelines emphasize open communication with risk managers and other interested parties to clearly convey information needed for decision making in a risk management context.

It is also EPA's policy that major scientifically and technically based work products related to the agency's decisions normally should be peer reviewed to enhance the quality and credibility of the agency's decisions. With regard to EPA's chemical risk assessments, peer review can be used for evaluating both specific assessments and the general methods EPA uses in its risk assessments. Peer review generally takes one of two forms: (1) internal peer review by a team of relevant experts from within EPA who have no other involvement with respect to the work product that is to be evaluated or (2) external peer review by a review team that consists primarily of independent experts from outside EPA. In December 2000, EPA released a revised edition of its *Peer Review Handbook* for use within the agency.

Chemical Risk Assessment at the Food and Drug Administration

The Food and Drug Administration (FDA) within the Department of Health and Human Services regulates the safety of a large number and wide variety of consumer products, including foods, cosmetics, human and animal medicines, medical devices, biologics (such as vaccines and blood products), and radiation-emitting products (such as microwave ovens). Chemical risk assessments are primarily conducted by three of FDA's five product-oriented centers—the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Veterinary Medicine (CVM), and the Center for Devices and Radiological Health (CDRH). The chemical risk assessment activities of these centers vary depending on factors such as the underlying statutory requirements, the substances being regulated, whether cancer or noncancer effects are of concern, and whether a product is under pre- or postmarket scrutiny. FDA officials said that the agency generally follows the National Academy of Sciences' (NAS) four-step risk assessment process, although it has not developed written internal guidelines. FDA often incorporates conservative assumptions into its assessments when information essential to a risk assessment is not known, but such assumptions are supposed to be scientifically plausible and consistent with agency regulations or policies. For example, CFSAN assumptions are expected to be reasonably protective of human health. FDA does not have an official policy on how risk assessment results should be characterized and communicated to policymakers and the public. However, FDA officials said that, in practice, they use a standard approach that typically highlights the assumptions with the greatest impact on the results of an analysis, states whether the assumptions used were conservative, and shows the implications of different choices.

Context for FDA Chemical Risk Assessment

FDA's regulatory authority is primarily derived from the Federal Food, Drug, and Cosmetic Act, as amended (FFDCA), although several related public health laws (e.g., the Food and Drug Administration Modernization Act of 1997, or FDAMA) provide additional authority. FDA administers its regulatory responsibilities through its five product-oriented centers: (1) CFSAN, (2) CVM, (3) CDRH, (4) the Center for Drug Evaluation and Research, and (5) the Center for Biologics Evaluation and Research. FDA officials said that, although each of these five product centers conducts some type of risk assessments, the first three primarily conduct the chemical risk assessments that are the focus of this report.[1] Each of these centers has different responsibilities, authorities, and constraints on its regulatory and risk assessment activities.

[1]Some of the offices focused on in this appendix also conduct other, nonchemical, types of risk assessments. For example, the Center for Devices and Radiological Health also uses risk assessments to determine the carcinogenic, genetic, and/or reproductive health risks associated with radiation-emitting products. The Center's reviews of medical devices are also likely to consider engineering risk assessments and the potential adverse effects of exposure to microbial contamination. The Center for Veterinary Medicine and the Center for Food Safety and Applied Nutrition also carry out microbiological risk assessments.

- CFSAN is responsible for the regulation of food additives, color additives used in food, and cosmetic additives.[2] Under the FFDCA, the regulation of substances intentionally added to food or used in contact with food must be based solely on the safety of the substances for their intended uses (i.e., consideration of benefits and costs is not allowed). A food containing an unapproved food or color additive is considered "unsafe" unless FDA issues a regulation approving its use or, in the case of a food contact substance, there exists an effective notification.[3] To obtain an authorizing regulation or an effective notification, the sponsor of a food or color additive must show that it is safe for its intended use. FDA regulations under the FFDCA define a product as safe if there is "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."[4] For food additives and color additives that are not themselves carcinogenic but contain carcinogenic impurities, CFSAN uses a quantitative risk assessment to determine whether the risk posed by a carcinogenic impurity is acceptable (i.e., a lifetime risk below one per million) under the FFDCA's general safety clause of "reasonable certainty of no harm." Nevertheless, if the food or color additive itself is a known carcinogen, under the "Delaney Clause" amendments to FFDCA, it cannot be deemed safe and is prohibited from use in food.[5] CFSAN is also involved with substantial activities in the area of postmarket concerns with contaminants and naturally occurring toxicants. For example, in the past year, CFSAN participated in a number of major, international chemical risk assessments in the areas of dioxins and various mycotoxins.

[2]FDA's responsibility in the food area covers all food except meat, poultry, and egg products, which are under the authority of the U.S. Department of Agriculture. Generally, FDA regulates food products sold in interstate commerce, whereas products made and sold entirely within a state are regulated by that state.

[3]Section 309 of FDAMA of 1997.

[4]21 CFR 170.3(i).

[5]21 U.S.C. 348 (c)(3)(A) on food additives and 379e(b)(5)(B) on color additives. The Food Quality Protection Act of 1996 eliminated application of the Delaney proviso to pesticides.

- CVM's primary role is to implement the FFDCA requirement that animal drugs and medicated feeds are safe and effective for their intended uses and that food from treated animals is safe for human consumption. Under the FFDCA, the regulation of residues of animal drugs that become a part of food because of the use of the animal drug must be based solely on health factors (i.e., consideration of benefits and costs is not allowed). A carcass or any of its parts that contain residues of an unapproved drug, or residues of an approved drug above approved levels, is considered to be unsafe and the carcass is considered adulterated. CVM uses risk assessment to help develop safe concentration levels in edible tissues, residue tolerances for postmarket monitoring, and withdrawal periods for slaughter following drug treatment. For noncancer effects, the applicable safety standard under FFDCA is that that these concentrations, tolerances, and withdrawal periods should represent a "reasonable certainty of no harm." FFDCA includes provisions that permit FDA to authorize extralabel uses of an animal drug that would pose a "reasonable probability" of risk to human health if residues of the drug are consumed. The agency may establish a safe level for the residue and require that the drug sponsor provide an analytical method for detecting residues of such a compound.[6] However, the act prohibits use in food-producing animals of any compound found to induce cancer when ingested by people or animals unless it can be determined that "no residue" of that compound will be found in the food produced from those animals under conditions of use reasonably certain to be followed in practice.[7] FDA has interpreted the intention of the "no residue" language in the statute as meaning that any remaining residues should present an insignificant risk of cancer to people. As a matter of policy, FDA accepts a lifetime risk below one per million as an insignificant level.

[6]21 U.S.C. 360b(a)(4)(B).

[7]21 U.S.C. 360b(d)(1)(I) on new animal drugs. This is known as the DES (diethylstilbestrol) proviso to the Delaney Clause. The Center for Veterinary Medicine's regulation found in 21 CFR 500.80 outlines how the center regulates carcinogenic drugs and feed additives under the DES proviso.

- CDRH administers the medical device provisions of FFDCA, and assesses risks posed by chemicals that might leach out from medical devices (e.g., breast implants) into surrounding tissue. The center's basic mission is to protect the public health by ensuring that there is reasonable evidence of the safety and effectiveness of medical devices intended for human use. CDRH usually evaluates risks in the context of a premarket review system, and the decision to clear or approve a product to treat a specific condition is based on a benefit-risk analysis for the intended population and use (not just on the basis of safety or human health as in the case of food regulation). Because all medical products are associated with risks, CDRH considers a medical product to be safe if it has reasonable risks given the magnitude of the benefit expected and the alternatives available.[8]

Another unit of FDA, the National Center for Toxicological Research (NCTR), has an important supporting role in the risk-related activities of the product centers. NCTR conducts much of the agency's methodological research on risk assessment methods and helps to develop and modify FDA's quantitative methods, in conjunction with experts from the various product centers. NCTR also provides toxicology research supporting all components of FDA. It performs fundamental and applied research designed specifically to define biologic mechanisms of action underlying the toxicity of products regulated by FDA.

[8]This applies to all medical products, including drugs and biological products, not just to devices.

Risk Assessment Procedures

Although FDA has long been a pioneer in the development of risk assessment methods, the agency has not developed written internal guidance specifically on conducting risk assessments. [9] FDA officials noted that much of their work is done before products are placed on the market and, in those instances, the burden of proof is on sponsors seeking FDA approval for new products.[10] In keeping with this requirement, FDA produces extensive external guidance documents that are primarily directed at those sponsors.[11] The documents are meant to represent the agency's current thinking on the scientific data and studies considered appropriate for assessing the safety of a product. However, the guidance documents are not legal requirements and do not preclude the use of alternative procedures or practices by either FDA or external parties. Some of these guidelines include detailed descriptions of risk assessment methods deemed appropriate to satisfy FDA's reviews under various statutory provisions. FDA has also adopted a number of domestic and international consensus standards that prescribe certain risk assessment methods (e.g., approaches for assessing the safety of medical devices and default consumption values for meat products).

[9]FDA published "Procedures for the Appraisal of Toxicity of Chemicals in Food," the agency's first guidance to industry, in 1949. In the 1950s, FDA initially developed the general NOAEL (or NOEL)/safety factor approach to noncancer risk assessment that has been used by most regulatory bodies (e.g., EPA's reference dose approach).

[10]This is not true with regard to dietary supplements. The Dietary Supplement Health and Education Act of 1994 created a new framework for FDA's regulation of dietary supplements, which do not have to undergo preapproval by FDA to determine their safety or efficacy. FDA officials said they currently have no standard procedures for dietary supplement risk assessment.

[11]Examples of such guidelines include "Redbook 2000: Toxicological Principles for the Safety of Food Ingredients," "Estimating Exposure to Direct Food Additives and Chemical Contaminants in the Diet," and "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals."

FDA risk assessment procedures have also been described by individuals and organizations from within and outside of the agency in scientific and professional journal articles. For example, a 1997 journal article written by a panel of officials from across FDA summarized the risk assessment approaches of each of FDA's product centers.[12] A 1996 report on federal agencies' chemical risk assessment methods described CFSAN's methods, but did not describe the approaches used by the other centers within FDA.[13] FDA's food safety risk assessment procedures were also described in "Precaution in U.S. Food Safety Decisionmaking: Annex II to the United States' National Food Safety System Paper," which was prepared for the Organization for Economic Cooperation and Development in March 2000.[14]

FDA officials said that the agency generally follows the four-step risk assessment process identified by NAS: hazard identification, dose-response assessment (which FDA prefers to call "hazard characterization"), exposure assessment, and risk characterization. They said that they also rely on past precedent and other seminal works on risk assessment, such as the 1985 Office of Science and Technology Policy guidance document on cancer risk assessment. However, they emphasized that FDA does not presume there is a "best way" of doing a risk assessment and is continually updating its procedures and techniques with the goal of using the "best available science."

Differences in Risk Assessment Among FDA Product Centers

FDA officials also said that there are variations in the risk assessment approaches used among the agency's different product centers and, in some cases, within those centers. In general, those variations are traceable to differences in the following factors:

- the substances being regulated,

[12]D.W. Gaylor, J.A. Axelrad, R.P. Brown, J.A. Cavagnaro, W.H. Cyr, K.L. Hulebak, R.J. Lorentzen, M.A. Miller, L.T. Mulligan, and B.A. Schwetz, "Health Risk Assessment Practices in the U.S. Food and Drug Administration," *Regulatory Toxicology and Pharmacology* 26 (1997).

[13]Lorenz R. Rhomberg, *A Survey of Methods for Chemical Health Risk Assessment Among Federal Regulatory Agencies*, a report prepared for the National Commission on Risk Assessment and Risk Management (1996).

[14]Hereinafter referred to as *Precaution in U.S. Food Safety Decisionmaking*. This paper also addresses risk assessment practices of other federal agencies involved in food safety, such as the Department of Agriculture and EPA.

- the nature of the health risks involved (particularly carcinogens versus noncarcinogens),
- statutory and regulatory requirements,
- whether the risk assessment is part of the process to review and approve a product before it can be marketed and used (premarket) or whether the assessment is for risks that might arise during monitoring of a product once it is being used (postmarket), and
- the nature and extent of the scientific information available.

The nature and extent of scientific information varies on a case-by-case basis. The other factors, however, are more generic, and table 6 illustrates how they are similar or different across CFSAN, CVM, and CDRH. The subsections following the table describe more specifically how CFSAN, CVM, and CDRH conduct the first three stages of risk assessment.

Table 6: Differences in FDA Chemical Risk Assessment Factors

	Nature of chemical health risk		Statutory/regulatory requirements		Stage of product review
Product center	**(Endpoint of concern)**	**Substances being regulated**	**Safety standard**	**Risk assessment mandated?**	**(Premarket/ Postmarket review)**
CFSAN –Office of Food Additive Safety	Noncancer toxicological endpoints	Food contact substances, direct and indirect food additives, color additives, and impurities	Reasonable certainty of no harm	Mandatory	Primarily premarket
CFSAN –Office of Food Additive Safety and Office of Nutritional Products, Labeling and Dietary Supplements	Various toxicological endpoints, including cancer	Industrial and naturally occurring chemical contaminants, dietary supplements	May render injurious to health In addition, for dietary supplements, significant or unreasonable risk of illness or injury	Mandatory for new dietary ingredients Discretionary for other food	Postmarket for foods Premarket for new dietary ingredients in dietary supplements

Product center	Nature of chemical health risk (Endpoint of concern)	Substances being regulated	Statutory/regulatory requirements: Safety standard	Statutory/regulatory requirements: Risk assessment mandated?	Stage of product review (Premarket/ Postmarket review)
CFSAN –Cancer Assessment Committee and Quantitative Risk Assessment Committee	Cancer	Direct and indirect food additives, food contact substances, color additives, and impurities	For additives, Delaney clause applies (carcinogens prohibited) For others, reasonable certainty of no harm standard applies	Assessment for carcinogenicity is mandatory as part of the premarket approval process, but a risk assessment is discretionary	Primarily premarket, but can (and has been) used for postmarket issues
CVM	Various noncancer toxicological endpoints	Residues of new animal drugs and feed additives	Reasonable certainty of no harm	Mandatory	Primarily premarket, but can (and has been) used for postmarket issues
CVM	Cancer	Residues of new animal drugs, feed additives, or their impurities	Reasonable certainty of no harm with inclusion of Delaney clause and DES proviso	Mandatory	Primarily premarket, but can (and has been) used for postmarket issues
CDRH	Cancer and noncancer endpoints	Chemical compounds released (leaching) from medical devices	Reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the labeling thereof In addition, regarding Class III premarket approval, unreasonable risk of illness or injury	Mandatory for certain types of devices (Class III), discretionary for others	Primarily premarket, but also could occur per postmarket surveillance

Source: Compiled from information provided by FDA.

CFSAN Risk Assessment Procedures

CFSAN's procedures for hazard identification and dose-response assessment vary depending on whether noncancer or cancer risks are at issue. For noncancer effects, CFSAN starts with the largest dose in a chronic animal study that did not appear to lead to an increase in toxic effects above the level measured in unexposed control animals— the "no observed adverse effect level" or NOAEL.[15] CFSAN then divides this NOAEL by one or more safety factors to arrive at an "acceptable daily intake" (ADI) intended to be an amount that can be ingested daily for a lifetime without harm. For example, CFSAN typically divides the NOAEL by 10 to allow for the possibility that humans might be more sensitive to a chemical than the experimental animals and then by another 10 to account for the possibility that some individuals might have greater sensitivity than others might. Therefore, for ADIs derived from long-term animal studies, CFSAN commonly uses a combined safety factor of 100. Additional safety factors may also be applied to account for long-term effects versus short-term experiments, inadequacies of the experimental data, or other factors.[16]

For cancer effects, CFSAN uses two different hazard assessment/dose-response approaches, depending on the nature of the products being regulated.

[15]FDA often determines a no observed effects level (NOEL) rather than a NOAEL because many significantly altered, standard toxicological endpoints are assumed to be adverse to animals and/or humans even in the absence of data affirming that assumption.

[16]For example, Lorenz Rhomberg noted that, for developmental toxicity, the Center for Food Safety and Applied Nutrition may use a combined safety factor of 1,000 for severe, irreversible health effects.

- For food and color additives that are themselves known carcinogens, the Delaney provisions in FFDCA make risk assessment rather straightforward. If a petition to market a food ingredient contains an adequately conducted animal cancer study, and if results of that study indicate that the food ingredient produces cancer in animals, CFSAN identifies the substance as a carcinogen under the conditions of the study. No further corroboration or weight-of-evidence analysis is required, and there is no need for a detailed dose-response assessment, exposure assessment, or risk characterization for the purpose of determining a specific level of the carcinogenic substance in food that may be considered to be safe.[17]
- CFSAN uses more elaborate procedures for known or suspected carcinogenic impurities in food additives. The center's method for low-dose cancer risk estimation is similar to EPA's method (presented in app. II) on extrapolation for carcinogens (see fig. 3). On the dose-response curve of tumor incidence versus dose for a chemical, CFSAN chooses a point below which the data are no longer considered reliable, usually in the range of a tumor incidence of 1 percent to 10 percent. A straight line is drawn from the upper-confidence limit on the estimated risk at that point to the origin (i.e., zero incremental dose/zero incremental response). This provides the slope of the line used to provide upper-bound estimates of cancer risk at low doses. CFSAN does not specify a particular mathematical form for the dose-response relationship in the experimental dose range; the only requirement is an adequate fit to the data.

According to FDA officials, CFSAN risk assessors use one of two different methods in animal-to-human scaling when extrapolating this dose-response curve to the estimation of upper bounds on human risk. In one of the methods, CFSAN assumes that cancer risks are equal in animals and humans when doses are similar on a lifetime-averaged milligram/kilogram/day basis (i.e., body weight scaling). In the other method, CFSAN bases its interspecies dose scaling on body weight to the ¾ power (in the absence of information to the contrary). Although the literature suggests that scaling methods can have a significant impact on risk assessment results, FDA officials said that using one approach versus the other makes relatively little difference. Also, because tumor rates can be biased by intercurrent mortality in animal studies (i.e., some animals die

[17] FDA may do a detailed assessment for other purposes, such as helping to determine regulatory priorities.

during the study from causes other than the tumor type being investigated), CFSAN uses a statistical procedure to make adjustments for intercurrent mortality in testing and estimating tumor rates.

CFSAN procedures for exposure assessments to food and color additives are largely driven by the FFDCA requirement that the safety of a chemical compound be assessed in terms of the total amount of the compound in the diet. Therefore, to determine exposure, CFSAN risk assessors must consider all potential uses of the compound being reviewed. Similarly, in defining the allowable limits, the assessors must conclude that the sum total of all of these uses is within safe limits. CFSAN generally assumes in its exposure assessments that the compound is present at its maximum proposed use level in all foods in which it may be used, that any contaminants are present at residue levels established through chemical analysis, and that consumers are exposed to the additive every day. Although most of the agency's focus is on chronic (long-term) exposures, the agency must also sometimes focus on very short-term, or even single, exposures, especially for contaminants associated with acute toxic effects.

The first component in CFSAN's exposure assessment for food safety is the determination of the concentrations (i.e., use levels or residue levels, in the case of a chemical contaminant) of a chemical in foods. In the premarket approval process, the sponsor of the petition or notification provides this information. For postmarket assessments, information may come from focused field surveys or from established monitoring programs such as the Total Diet Study, which has provided data since 1961 on dietary intakes of a variety of food contaminants, including pesticides, industrial chemicals, toxic and nutritional elements, and vitamins and radionucleides. Analyses are performed on foods prepared for consumption in order to provide a realistic measure of human intake.

The second component of CFSAN's exposure assessment is determining the extent of consumption of different foods. In this process, CFSAN primarily relies on multiple-day national food consumption surveys, and focuses on the upper end of the food intake distribution (i.e., the heaviest consumers of particular foods). CFSAN assumes that, within demographic subgroups, all variation in the survey data represents variation among individuals. That is, the average daily consumption of a food during the survey period is assumed to apply to that person for his or her whole life, and the intakes for different survey participants are assumed to reflect differences from one person to the next in each person's lifetime consumption. This default assumption has acknowledged biases that result in both overestimating high-end chronic exposures and underestimating the proportion of the population ever consuming particular foods.[18]

To complete the exposure assessment, levels of an additive or contaminant in each food type are combined with estimates of daily consumption of each food type to give a total estimated daily intake. FDA may calculate exposures for various demographic groups, attempting to characterize both a mean exposure and an exposure for the heavy consumer (typically consumers at the 90th percentile of the intake distribution). FDA officials also pointed out that the exposure models they use for direct food additives are very different from those for food-contact substances (e.g., packaging).[19] For the latter, they said that the bottom line is usually a mean exposure.

[18]EPA's pesticide office uses an alternative assumption—that surveyed variation represents day-to-day variation. Using this assumption, the exposure estimate represents average chronic consumption, but fails to estimate high-end exposures.

[19] See CFSAN's "Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations."

FDA officials said that for risk management purposes they may attempt to show the implications of different scenarios used to estimate risk. FDA noted that a computer program that employs Monte Carlo techniques has been developed to study the effects of variability and uncertainty of potency and exposure estimates on estimates of risk.[20] Such complex analyses have been applied principally to contaminants rather than in the premarket evaluations for food and color additives.

CVM Risk Assessment Procedures

CVM uses risk assessment in both the premarket approval process and postmarket surveillance. Risk assessments support risk management decisions such as the development of safe concentration values and residue tolerances for these drugs in foods. The primary human health concern in chemical risk assessment for CVM is animal drug residues in food. Residue is defined as any compound present in edible tissues (including milk and eggs) of the food-producing animal that results from the use of the chemical compound, including the compound, its metabolites, or other substances formed in or on food because of the use of the compound.

Like CFSAN, CVM's risk assessment procedures vary based on whether noncancer or cancer risks are at issue. According to FDA officials, the center's risk assessment procedures for noncarcinogens are similar to those used by the rest of FDA, and are based on laboratory animal data, estimated daily food consumption, drug and metabolite residue data, and appropriate safety factors. CVM's guidelines for industry note that the agency will calculate the ADI from the results of the most sensitive study in the most sensitive species. The center will normally use different safety factors depending on the type of study supporting the ADI calculation. When using the ADI to calculate the "safe concentration" for an animal drug product, CVM uses standard values for residues of veterinary drugs in edible tissues for the weight of an average adult and the amount and proportion of meat products, milk, and eggs consumed per day. CVM officials pointed out that the consumption values in their guidelines for industry are standard values used by the Joint Expert Committee on Food Additives, sponsored by the World Health Organization and Food and

[20]Monte Carlo analysis involves a repeated random sampling from the distribution of values for each of the parameters in a calculation (such as average daily exposure) to derive a distribution of estimates of exposures for a population. According to FDA, because Monte Carlo modeling is a probabilistic technique that can use all the available food intake and concentration data, it will result in more accurate estimates at upper percentiles of exposure than those obtained using point values from consumer surveys.

Agriculture Organization, that provides food safety recommendations to the Codex Committee on Residues of Veterinary Drugs in Foods.

For carcinogen risk assessments, CVM uses a nonthreshold, conservative, linear-at-low-dose extrapolation procedure to estimate an upper limit of low-dose risk (as described under CFSAN). Cancer risk estimates are generally based on animal bioassays, and upper 95-percent confidence limits of carcinogenic potency are used to account for inherent experimental variability. FDA officials noted that some elements and assumptions of its dose-response analysis procedures are likely to overestimate risk by an unknown amount. Similarly, some of its assumptions on exposure may also overestimate cancer risks. For example, CVM's risk assessment procedures assume that the concentration of residue in the edible product is at the permitted concentration and that consumption is equal to that of the 90th percentile consumer. In addition, the agency assumes that all marketed animals are treated with the carcinogen. While acknowledging that all of these assumptions result in multiple conservatisms, FDA also states that they are prudent because of the uncertainties involved.

CDRH Risk Assessment Procedures

Medical devices, supplies, and implants may contain chemicals that can leach out of the devices into surrounding tissues. Risks from these types of chemical contaminants are considered during the premarket review of the material safety of a device, but concerns may also arise during CDRH's postmarket surveillance activities.[21] According to FDA officials, the concentrations of such leachants in human tissues are generally small and amenable to typical safety risk assessment procedures.

[21]As an example of a postmarket quantitative risk assessment, FDA cited its assessment of cancer risk posed by patient exposure to 2,4-toluenediamine released from polyurethane foam-covered breast implants.

CDRH has issued guidance for the preclinical (premarket) biological safety evaluation of medical devices.[22] In that guidance, CDRH recognizes and uses a number of domestic and international consensus standards that have been developed to address aspects of medical device safety, including risks posed by exposure to compounds released from medical devices. However, CDRH officials pointed out that they and medical device approval applicants may use approaches other than those described in the consensus standards to conduct risk assessments. They said the standard that comes closest to describing CDRH's approach for chemical risk assessment is International Organization for Standardization (ISO)/FDIS 10933-17.[23] CDRH officials noted that, although this international standard is still in draft and has not been formally recognized by the center, the methods that it describes represent the primary procedures used by CDRH to assess the risk posed by patient exposure to compounds released from medical devices. They also pointed out that this standard is unique among risk assessment guidelines in that it provides methods to derive health-based exposure levels for local effects such as irritation, which often "drive" the risk assessment for compounds released from implanted devices.

According to CDRH, hazards posed by patient exposure to a device are typically determined after subjecting the device to a series of tests defined by the preclinical evaluation guidance. Evaluation of potential toxicity is supposed to cover a number of adverse effects, including local or systemic effects, cancer, and reproductive and developmental effects. Unless justification is otherwise provided, CDRH assumes that the results obtained in animal studies are relevant for humans. One notable exception for medical device risk assessment, according to CDRH, is that implantation-site sarcomas (malignant tumors) found in rodents are not assumed to be relevant for humans.

One option available to applicants is to use a risk assessment approach involving: (1) characterization of the chemical constituents released from a

[22]The Center for Devices and Radiological Health's Office of Device Evaluation "Blue Book" memorandum #G95-1, "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part-1: Evaluation and Testing.'"

[23]Biological evaluation of medical device –Part 17: Methods for the establishment of allowable limits for leachable substances. The International Organization for Standardization is a nongovernmental federation of national standards bodies from about 140 countries. Its work results in international agreements that are published as international standards.

device; (2) derivation of a tolerable intake (TI) value for the compound; and (3) comparing the dose of each constituent received by a patient to its respective TI value. A TI value is a dose of a compound that is not expected to produce adverse effects in patients following exposure to the compound for a defined period. According to CDRH, it is conceptually similar to EPA's reference dose, but different TI values can be derived for a compound depending on the route and duration of exposure to the medical device.

CDRH's procedures recommend establishing TI values for noncancer adverse effects using standard uncertainty factors in order to account for interspecies and inter-individual differences in sensitivity. However, CDRH permits flexibility in the event that data are available to characterize these uncertainties more accurately. CDRH also uses a lumped uncertainty factor to adjust for limitations in data quality such as (1) the use of short-term studies in the absence of long-term studies, (2) the absence of supporting studies, and (3) use of studies involving different routes or rates of exposure. According to CDRH, this lumped uncertainty value typically does not exceed 100, but can exceed 100 when acute (short-term) toxicity data are the only basis of the calculation of a TI value for permanent exposure. CDRH considers this provision especially important for medical device risk assessment because of the paucity of long-term toxicity data for many of the compounds released from medical devices.

For carcinogenic leachants, FDA often uses low-dose linear extrapolation techniques. For a device-released compound that has been determined to be a carcinogen, CDRH uses a weight-of-the-evidence approach to determine the likelihood that it exerts its carcinogenic effect via a genotoxic mechanism.[24] If the evidence suggests that the compound is genotoxic, then CDRH uses quantitative risk assessment to estimate a TI consistent with a risk level of 1 per 10,000. No specific quantitative risk assessment approaches have been identified as better than others for conducting the cancer risk assessment. If, however, the weight-of-the-evidence test suggests that the compound is a nongenotoxic carcinogen, the uncertainty factor approach described above should be employed to derive the TI.

[24]A genotoxic carcinogen is one that initiates cancer through a direct effect on genetic material. It is capable of causing heritable changes or damage leading to heritable changes in genetic material.

Once the TI is derived for each compound released from a device, it is then converted to a tolerable exposure value by taking into account the body weight of the patient and the usage patterns of the device that releases the compound. Overall, the agency noted that one of the most challenging problems in risk assessments for devices is determining the level of exposure to leached chemicals.

Risk Assessment Assumptions and Methodological Choices

As previously noted, FDA does not require the use of a specific risk assessment protocol or of specific default assumptions. However, the summary of FDA procedures also demonstrated that assumptions and methodological choices are an integral part of a risk assessment. FDA officials noted that they employ many default assumptions or choices by precedent. In particular, FDA officials and several reference documents on FDA risk assessment procedures pointed out that the agency routinely incorporates conservative assumptions into its assessments in the face of uncertainty. The report on the U.S. food safety system emphasized that precaution is embedded in the underlying statutes and the actions of regulatory agencies to ensure acceptable levels of consumer protection.[25] Therefore, precautionary approaches are very much a part of the agency's risk analysis policies and procedures.

Although not intended to be comprehensive, the following table illustrates in detail some of the specific assumptions or methodological choices that are used in FDA as a whole and within particular FDA product centers. The information in the table was taken primarily from FDA documents, but also reflects additional comments provided by FDA officials. (GAO notes and comments appear in parentheses.)

[25]*Precaution in U.S. Food Safety Decisionmaking.*

Table 7: FDA Risk Assessment Assumptions and Methodological Choices

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
(Methodological assumptions and choices in general.)	According to FDA officials, "reasons" always include the following three general items: • information essential to a risk assessment is not known; • the assumption, selected by FDA to substitute for that information, is scientifically plausible; and • the effect of using the assumption is consistent with agency regulations or policy (e.g., for CFSAN, an assumption is expected to be reasonably protective of human health).	According to FDA officials, the circumstances under which these assumptions would be used always include that data indicating the assumption may be invalid for a particular circumstance are not available.	(Not applicable to this generic information.)
1. CFSAN general procedures regarding food safety			
1.1 Animal studies are useful for human risk assessment, with appropriate uncertainty factors (i.e., you can extrapolate human effects from animal data).	This is a fundamental assumption of quantitative risk assessment, accepted as a basic precedent according to FDA officials. They noted that, in general, adequate information from human studies is preferred to adequate data from animal studies. However, when human data are not available, or when such data are judged to be relatively insensitive to moderate- or low-level risks and difficult to quantify, FDA makes the assumption that animal studies can be used for human risk assessment. FDA officials also said that the application of appropriate uncertainty factors to data from animal studies makes this assumption reasonably protective of human health.	When there are no data or inadequate data on human outcomes.	For chemicals that are human carcinogens, animal data may underestimate human risk by up to one order of magnitude and overestimate risk by up to three orders of magnitude [citations provided].

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.2 Use the most sensitive animal species, unless you have information to the contrary.	(Not identified in the FDA documents that we reviewed describing risk assessment procedures. However, FDA officials explained that comparative absorption, metabolism, distribution, and elimination data could identify the most appropriate animal model for extrapolating results from animals to humans. They also stated that FDA has determined that use of this assumption is reasonably protective of human health.)	When choosing which animal study data to use for hazard identification and dose-response estimation, when the most appropriate animal model for humans is not known.	(Not specifically identified, but FDA officials commented that risk assessment literature identifies the "usual" range of toxicological responses among animal models for this assumption.)
1.3 You can extrapolate low-dose effects from high-dose effects.	FDA officials identified this assumption as another fundamental assumption, similar to 1.1 above, noting that, in general, low-dose effects cannot be directly measured in human epidemiology studies or in animal toxicity and carcinogenicity studies. They said that, in such circumstances, the mechanism of action at low doses is assumed to be the same as that operating at higher doses, which makes the related assumption that one can extrapolate effects at low doses from effects at high doses scientifically plausible. FDA has determined that such an assumption is reasonably protective of human health.	When doing low-dose extrapolation because low-dose effects were not directly measured in available human or animal studies and the mechanism of action at low doses is not known to be different than the mechanism at higher doses.	(Not explicitly identified. FDA officials explained that the literature on this subject shows "very large" variability among predictions of low-dose effects using different modeling assumptions. They also stated that, because they do not know the correct relationship between high-and low-dose effects for a substance, they do not know how much conservatism is associated with the use of this assumption.)

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.4 Low-dose cancer risk estimation is done using a linear, no-threshold approach. The point of departure for this linear extrapolation is the upper-confidence limit on risk at a point on the dose-response curve below which the data no longer appear to be reliable. However, the agency does not specify any particular mathematical form for the dose-response relationship in the experimental dose range, just that there is an adequate fit to the data. A more specific, but related, string of assumptions is that genotoxic carcinogens do not have thresholds, and the appropriate low-dose extrapolation is linear.	Not specifically identified, but FDA noted in general that, because it is not possible to determine the accuracy and precision of low-dose cancer estimates, the agency employs conservative risk assessment procedures to compensate for weaknesses in scientific rigor. The agency did provide specific citations for various low-dose extrapolation procedures.	When doing low-dose extrapolation for carcinogens.	This linear extrapolation provides upper-bound estimates of cancer risk at low doses.
1.5 Dose scaling across species is based on body weight to the ¾ power (an adjustment factor for calculating the dose at which cancer risks are equal in rodents and humans) (In meetings with CFSAN officials, we were informed that the agency's risk assessors may also use the default that cancer risks are presumed equal when daily amounts of a chemical agent are scaled in proportion to a species' body weight.)	The ¾ power approach was recommended in a 1992 proposed rule by an interagency committee [citation provided].	When extrapolating equivalent doses of a carcinogen from animals to humans, in the absence of information to the contrary.	(Not addressed in FDA materials, but other sources indicated that the "body weight ¾ power" approach is considered to produce the midpoint of plausible values from among the common alternative approaches for interspecies dose scaling, while "body weight" scaling is considered to produce the least conservative values. A CFSAN official stated that this choice makes little difference in the results.)

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.6 FDA/CFSAN uses a basic no observed effect level (NOEL) safety factor approach for noncancer effects. The agency generally uses standard safety factors to account for uncertainty: a. A safety factor of 10 is used to account for the possible increased sensitivity of humans compared to test animals. b. Another safety factor of 10 is used to account for the increased sensitivity of some humans. c. Additional safety factors are often employed to account for long-term effects based on short-term experiments, use of a LOAEL instead of a NOEL/NOAEL, and other inadequacies of the experimental data.	(Note that the underlying statute specifically directs the use of safety factors.)	Risk assessments for noncancer endpoints –estimating an ADI from the results of animal experiments.	The resulting ADI is an estimate with uncertainty spanning perhaps an order of magnitude of a daily exposure that is likely to be without appreciable risk of deleterious effects during a lifetime.

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.7 CFSAN uses a series of assumptions about food consumption: a. The agency assumes that the average total diet of a 60-kg adult generally consists of 1500 grams (g) of solid food and 1500 g of liquid per day. b. For calculating exposure to additives or contaminants, CFSAN frequently uses the 90th percentile of consumption to represent intake of heavy consumers. c. In the absence of the distribution of intakes among individuals in a population and a direct measure of the 90th percentile, the 90th percentile is estimated to be two to three times the average intake.	a. Empirical: based on food consumption survey data. b. Concern that the mean exposure is not sufficiently public-health conservative. c. The method for estimating the 90th percentile in the absence of other data is based on observations from dietary survey distribution data for a variety of products.	Assumptions about consumption used when estimating human exposure to chemical substances (i.e., additives, residues) in foods.	FDA officials told us that these assumptions provide a public-health conservative estimate of exposure for comparison with the ADI.
1.8 The agency usually assumes that, within demographic groups, food intake survey variation represents differences in chronic consumption among individuals. The average daily consumption by an individual of a food during the survey period is assumed to apply to that person for his or her whole life.	FDA officials said they use this assumption because only short-term food intake surveys are available.	When basing exposure estimates on food intake surveys.	According to the Rhomberg report, the effect of this assumption is an acknowledged overestimation of high-end chronic exposures and an underestimation of the proportion of the population ever consuming particular foods.

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1.9 The agency generally assumes that all foods in which a chemical additive is proposed or permitted for use will bear it at the maximum proposed or permissible use level. The agency also assumes that consumers are exposed to an additive every day for a lifetime.	FDA officials said that they use these public-health conservative assumptions because of the lack of scientifically sound information that would permit their relaxation.	When doing exposure assessments.	FDA officials said these assumptions were public-health conservative.
1.10 When dealing with mixtures of carcinogens, the agency usually considers that interactions are not likely and uses some standard assumptions: a. It is assumed that carcinogens are acting independently. Therefore, the risk of cancer from a mixture may be obtained by summing the individual risk. b. It is generally assumed that all carcinogenic components are at their tolerance concentrations.	The agency noted that its intent is to be conservative, and it cited research on the estimation of upper-confidence limits on estimates of risk for mixtures.	When doing risk assessments involving mixtures of chemicals (with dose levels for each component below those having measurable effects for that compound).	The intent is to be conservative.

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
2. CVM procedures regarding animal drug residues in food			
2.1 As a matter of policy regarding potential risks from residues of carcinogenic animal drugs in foods consumed by humans (per the DES Proviso to the Delaney Clause), FDA accepts a lifetime risk below one per million as an insignificant level.	In general, FDA noted that all of the assumptions identified in this section on the DES Proviso (see following rows 2.2 through 2.5), "result in multiple conservatisms, but are prudent because of the uncertainties." "Thus, adoption of a [residue] concentration associated with a cancer risk of one per million is likely to be well below that level of risk and to satisfy the FDA's responsibility under the statute [FFDCA] to ensure to a reasonable certainty that the public will not be harmed."	When conducting cancer risk assessments.	This set of assumptions was identified generically as "resulting in multiple conservatisms."
2.2 Regulation is based on the target tissue site exhibiting the highest potential for cancer risk for each carcinogenic compound. If tumors are produced at more than one tissue site, the minimum concentration that produced a tumor is used.	(No additional information provided, but see row 2.1 for general rationale.)	Choosing data sets to use for cancer risk assessments.	(See previous row.)

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
2.3 Cancer risk estimates are generally based on animal bioassays, using upper 95-percent confidence limits of carcinogenic potency. Low-dose extrapolation is done using a nonthreshold, conservative, linear-at-low-dose procedure (modified Gaylor-Kodell).	Upper 95-percent confidence limits are used to account for inherent experimental variability. The low-dose extrapolation procedure estimates an upper limit on low-dose risk. In its general principles for industry (guideline #3), CVM notes that none of the mathematical procedures for extrapolation has a fully adequate biological rationale, because the mechanism of carcinogenesis is not sufficiently understood.	When doing low-dose extrapolation from animal bioassay data in the absence of information establishing the mechanism of carcinogenesis of a compound.	The process of linearly extrapolating from the high doses used in animal bioassays to concentrations of residues is likely to overestimate risk by an unknown amount.
2.4 It is assumed that the carcinogenic potency in humans is the same as that in animals.	(No additional information provided, but see row 2.1 for general rationale.)	In cancer risk assessments when doing low-dose extrapolation from animal bioassay data.	From rather limited data comparing human and animal cancer potencies of compounds, animal results are likely to overestimate human cancer risk but could underestimate risk by an order of magnitude (citations provided).

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
2.5 Multiple assumptions are used in carcinogen exposure assessments: a. The concentration of residue in the edible product is at the permitted concentration. b. Consumption is equal to that of the 90th percentile consumer. c. All marketed animals are treated with the carcinogen. d. In the absence of information about the composition of the total residue in edible tissue, assume that the entire residue is of carcinogenic concern.	(See row 2.1 for general rationale. Note that item d is taken from CVM's guidance for industry.)	Used for exposure assessments for cancer risks.	These assumptions on exposures also overestimate the risk.
2.6 For noncancer toxicological endpoints, the agency will calculate the ADI from the NOEL of the most sensitive effect in an animal study of the most sensitive sex and species.	FDA officials said this assumption was used because of historical precedent back to at least 1954, because, in the absence of data (e.g., physiologically based pharmacokinetic or other data) suggesting that another species is more appropriate to use for extrapolating to humans, using the most sensitive endpoint in the most sensitive species and sex is still considered to be protective of public health.	In noncancer risk assessment, when calculating the ADI based upon animal studies and in the absence of data suggesting that an alternative approach is scientifically justified.	(Not identified, but the intent of this calculation is to provide protective, public-health conservative estimates.)

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
2.7 The agency will normally use the following safety factors, depending on the type of study supporting the ADI estimate: a. chronic study (factor of 100), b. reproduction/teratology study (100 for a clear indication of maternal toxicity; 1000 for other effects), and c. 90-day study (1000).	These are identified as "appropriate" safety factors.	In noncancer risk assessment when calculating the ADI by dividing the NOEL from an animal study by safety factors.	(Not identified, but the intent of such factors is usually to provide protective, public-health conservative estimates.)
2.8 The agency uses a series of standard values and assumptions to estimate an individual's daily food consumption: a. edible muscle (300 grams); b. liver (100 g); c. kidney (50 g); d. fat (50 g); e. assume that when an individual consumes a full portion of a meat product from one species, he or she will not consume a full portion of a meat product from another species; f. assume a person consumes a full portion of milk (1.5 liters) in addition to the full portion of edible muscle or organ tissue; and g. assume that a person consumes a full portion of eggs (100 g) in addition to the consumption of muscle or organ tissue.	CVM officials noted that the standard consumption factors (e.g., 300 grams of muscle) were established by the Joint Expert Committee on Food Additives (sponsored by the World Health Organization and the Food and Agriculture Organization of the United Nations).	Exposure analysis for noncancer risk assessments. Consumption values applied to determine the safe concentration for most new animal drug products, unless an appropriate scientific justification supports alternative consumption values.	(Not identified, but the intent of such factors is usually to provide protective, public-health conservative estimates.)

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
2.9 The agency assumes the weight of an average adult is 60 kg when calculating the safe concentration of a compound in edible tissue of a food-producing animal.	CVM officials said this assumption is used because of historical precedent and because the 60-kg person is likely to cover the exposure of women, growing adolescents, and the elderly.	CVM officials said that this assumption is applied in all circumstances.	CVM officials said the assumption should protect women, growing adolescents, and the elderly.
3. CDRH procedures regarding medical devices (For purposes of this report, limited to chemical leachants. Does not include engineering or radiation risk assessments.)			
3.1 CDRH assumes that the results obtained in animal studies are relevant for humans, but with one notable exception for medical device risk assessment – implantation-site malignant tumors found in rodents are not assumed to be relevant for humans.	(Not specifically addressed in the material provided by CDRH, although the first part is a standard assumption of quantitative risk assessment.)	During hazard identification.	(Not mentioned.)
3.2 Extractions of medical devices (to test for adverse effects) are typically carried out using rigorous but not exhaustive conditions to provide a “safety factor” for the hazard identification phase.	To provide a safety factor.	During hazard identification.	(Not specifically identified, but the intent of such factors is usually to provide protective, public-health conservative estimates.)

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
3.3 The following uncertainty factors are typically used for adverse effects other than cancer: a. a factor to adjust for interspecies differences in sensitivity to toxic compounds; b. a factor to adjust for interindividual differences in sensitivity to toxic compounds; and c. a "lumped" factor to adjust for limitations in data quality.	The first two factors are standard uncertainty factors recommended in the scientific literature. The lumped uncertainty factor takes into account: 1. use of short-term studies in the absence of long-term studies; 2. having only a LOAEL instead of a NOAEL; 3. absence of supporting studies; 4. route-to-route extrapolation of dose, when needed; 5. rate of exposure; and 6. confidence in the data base. CDRH noted that the lumped factor typically does not exceed 100, but can exceed this value when acute toxicity data are the only basis for the calculation of a TI value for permanent exposure.	Used when calculating TI values for noncancer effects of chemical compounds, unless case data are available to characterize these uncertainties more accurately.	(Not specifically identified, but the intent of such factors is usually to provide protective, public-health conservative estimates.)

Source: Compiled from GAO review of FDA risk assessment guidelines and related documents and from additional comments provided by agency officials.

Risk Characterization

Unlike EPA, FDA does not have an official policy on how the results of the agency's risk assessments should be characterized to decision makers and the public. However, FDA officials said that, in practice, the agency uses a standard approach for risk characterization that is similar to EPA's official policy. They said that FDA's general policy is to reveal the risk assessment assumptions that have the greatest impact on the results of the analysis, and to state whether the assumptions used in the assessment were conservative. FDA officials also said that their risk assessors attempt to show the implications of different distributions and choices (e.g., the results expected at different levels of regulatory intervention). As noted earlier, FDA may employ methods such as Monte Carlo techniques to provide additional information on the effects of variability and uncertainty on estimates of risk.

There are some differences in FDA risk characterization procedures depending on the products being regulated and the nature of the risks involved. For food ingredients (direct and indirect food additives, color additives used in food, and substances generally recognized as safe) and animal drug residues that are not carcinogenic, risk characterization under the FFDCA focuses on whether the mandate of reasonable certainty of no harm will be achieved given the proposed limits on use and permissible residues. The main issue is whether the higher end (the 90th percentile) of the distribution of estimated daily intakes is below the ADI calculated from toxicity data. The statutory mandate is interpreted as requiring that, for a food additive to be declared safe, heavy consumers of particular foods should be reasonably assured of protection even if residues were at the maximum level allowed. For carcinogenic impurities, FDA's focus is also on characterizing whether there is reasonable certainty of no harm. However, because of the Delaney clause, risk characterization is not needed for carcinogenic food ingredients. Residues of carcinogenic animal drugs are also evaluated separately under the DES proviso.

CDRH officials pointed out that the draft ISO/FDIS 10933-17 international standard explicitly addresses one risk characterization issue—how sensitive subpopulations should be taken into account when setting allowable limits for compounds released from devices. Although it states that "idiosyncratic hypersusceptibility" should not normally be the basis of the tolerable exposure or allowable limit, the ISO standard does not preclude setting standards in this manner. Furthermore, the standard says that limits should be based on the use of the device by the broadest segment of the anticipated user population. Therefore, if a device is intended for a specific population, such as pregnant women, estimates should be based on that population.

Chemical Risk Assessment at the Occupational Safety and Health Administration

Although the Occupational Safety and Health Administration (OSHA) generally follows the standard four-step National Academy of Sciences' (NAS) paradigm for risk assessment, there are several distinguishing characteristics of its assessments. Under its statutory mandate, OSHA has a specific and narrow focus on the potential risks to workers in an occupational setting. Further, the underlying statute and court decisions interpreting the statute have required the agency to focus on demonstrating, with substantial evidence, that significant risks to workers exist before it can regulate. In addition to presenting its own best estimates of risk, OSHA may present estimates based on alternative methods and assumptions.

Context for OSHA Chemical Risk Assessment

Much of what is distinct about risk assessment at OSHA can be traced to statutory provisions, court decisions, and the nature of workplace exposures to chemicals. OSHA, an agency within the Department of Labor, was created by the Occupational Safety and Health Act of 1970 (the OSH Act).[1] The central purpose of the act is to ensure safe and healthful working conditions. As one of the primary means of achieving this goal, the act authorizes the Secretary of Labor to promulgate and enforce mandatory occupational safety and health standards.[2] Certain provisions in the act stipulate both the nature and the manner in which these standards should be established. For example:

- Under section 3(8) of the OSH Act, a safety or health standard is defined as a standard that requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide safe or healthful employment or places of employment.
- According to OSHA, a standard is reasonably necessary or appropriate within the meaning of section 3(8) if it eliminates or substantially reduces significant risk and is economically feasible, technologically feasible, cost effective, consistent with prior OSHA action or supported by a reasoned justification for departing from prior OSHA actions, supported by substantial evidence on the record as a whole, and is

[1] 29 U.S.C. 651 *et seq.*

[2] Safety standards are generally designed to reduce on-the-job injuries. Health standards are usually directed at limiting the risk of workers developing occupational diseases from exposure to hazardous chemical or physical agents.

better able to effectuate the act's purposes than any national consensus standard it supersedes.

- Section 6(b)(5) of the act states that "The Secretary, in promulgating standards dealing with toxic materials or harmful physical agents… shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life."

A significant factor influencing the interpretation of the OSH Act provisions and OSHA's approach to risk assessment is the Supreme Court ruling in its 1980 "Benzene" decision that, before issuing a standard, OSHA must demonstrate that the chemical involved poses a "significant risk" under workplace conditions permitted by current regulations and that the new limit OSHA proposes will substantially reduce that risk.[3] This decision effectively requires OSHA to evaluate the risks associated with exposure to a chemical and to determine that these risks are "significant" before issuing a standard. However, the court provided only general guidance on what level of risk should be considered significant. The court noted that a reasonable person might consider a fatality risk of 1 in 1000 (10^{-3}) to be a significant risk and a risk of one in one billion (10^{-9}) to be insignificant. Thus, OSHA considers a lifetime risk of 1 death per 1,000 workers to represent a level of risk that is clearly significant. The court also stated that "while the Agency must support its findings that a certain level of risk exists with substantial evidence, we recognize that its determination that a particular level of risk is significant will be based largely on policy considerations."[4]

Later Court of Appeals decisions have interpreted the Supreme Court's "Benzene" decision to mean that OSHA must quantify or explain the risk for each substance that it seeks to regulate unless it can demonstrate that a group of substances share common properties and pose similar risks.[5] Although this decision does not require OSHA to quantitatively estimate the risk to workers in every case, it does preclude OSHA from setting new

[3] *Industrial Union Dept. v. American Petroleum Inst.*, 448 U.S. 607, 642 (1980).

[4] 448 U.S. at 655-56 n.62.

[5] *AFL-CIO v. OSHA*, 965 F.2d 962 (11th Cir. 1992), *International Union, UAW v. Pendergrass*, 878 F.2d 389 (D.C. Cir. 1989).

standards without explaining how it arrives at a determination that the standard will substantially reduce a significant risk.

According to OSHA officials, the other important contextual influence on OSHA risk assessment is the very nature of workplace exposures to chemicals. Generally, workplace exposures to chemicals are at higher levels than most environmental exposures to chemicals experienced by the general public. Workers are often exposed to many chemical agents at levels not much lower than those used in experimental animal studies. According to agency officials, this is one of the unique features of OSHA's chemical risk assessments. Also, OSHA frequently has relevant human data available on current exposures, in contrast to most other agencies regulating toxic substances.

Risk Assessment Procedures

General Approach

OSHA currently has no formal internal risk assessment guidance. Instead, OSHA has primarily described its general risk assessment methods, as well as the rationale for specific models and assumptions selected, in the record of each risk assessment and regulatory action. One reason for this, according to agency officials, is that OSHA performs risk assessments only for its standards. Overall, they said the agency only publishes two or three proposed or final rules per year, and not all of these rules involve a chemical risk assessment. The officials also emphasized the incremental nature of advances in risk assessment methods and science, with successive assessments establishing precedents for methods that may be used for succeeding analyses.

Like EPA and FDA, OSHA uses the basic NAS four-step process for risk assessment. Another fundamental source for OSHA's (and EPA's and FDA's) methods was the 1985 document on chemical carcinogens produced by the Office of Science and Technology Policy.[6] OSHA often refers to the reference sources of other entities, including other federal agencies, in

[6] Office of Science and Technology Policy, Executive Office of the President, "Chemical Carcinogens: A Review of the Science and Its Associated Principles, February 1985," 50 FR 10372 (Mar. 14, 1985).

both specific rulemakings and as general technical links to its on-line information on occupational risks.

Despite these common elements and procedures, several features of OSHA's approach differ from those of other federal agencies. Because OSHA does not currently have written internal guidance on its risk assessment procedures, the information in the following sections is derived primarily from an examination of OSHA's chemical risk assessments.[7] We also relied on secondary sources, such as Lorenz Rhomberg's report on federal agencies' risk assessment methods.[8]

Hazard Identification

In OSHA's risk assessments, the hazard identification step results in a determination that an exposure to a toxic substance causes, is likely to cause, or is unlikely or unable to cause, one or more specific adverse health effects in workers. According to OSHA, this step also shows which studies have data that would allow a quantitative estimation of risk. OSHA defines hazardous and toxic substances as those chemicals present in the workplace that are capable of causing harm. In this definition, the term chemicals includes dusts, mixtures, and common materials such as paints, fuels, and solvents. OSHA currently regulates exposure to approximately 400 such substances. In the workplace environment, chemicals pose a wide range of health hazards (e.g., irritation, sensitization, carcinogenicity, and noncancer acute and chronic toxic effects) and physical hazards (e.g., ionizing and nonionizing radiation, noise, and vibration).

[7] Because OSHA's methylene chloride standard is the most recent hazardous chemical rulemaking, most of the specific examples cited come from OSHA's methylene chloride rulemaking: "Occupational Exposure to Methylene Chloride," 62 FR 1494 (Jan. 10, 1997).

[8] Lorenz R. Rhomberg, *A Survey of Methods for Chemical Health Risk Assessment Among Federal Regulatory Agencies*, a report prepared for the National Commission on Risk Assessment and Risk Management (1996).

Most of OSHA's chemical risk assessments have addressed occupational carcinogens. In assessing potential carcinogens, OSHA may consider the formal hazard classification or ranking schemes of other entities as part of the available evidence on a particular chemical. Ultimately, though, OSHA makes its own determinations on the risk posed by particular compounds and their classification as potential occupational carcinogens. OSHA's chemical risk assessments may also discuss noncancer hazards. For example, in the final rule on methylene chloride the agency discussed the evidence regarding central nervous system, cardiac, hepatic (liver), and reproductive toxicity, as well as carcinogenicity. Similarly, the agency's rulemaking on 1,3-butadiene addressed adverse health effects such as developmental and reproductive toxicity and bone marrow effects in addition to the evidence on carcinogenicity.[9] OSHA quantifies the risks of noncancer effects if it determines that there are adequate data on exposure and response for the substance of interest.

OSHA officials also noted that OSHA has a hazard communication standard, which requires manufacturers, shippers, importers, and employees to inform their employees of any potential health hazard when handling these chemicals. This is usually done through container labeling and material safety data sheets. Although this standard does not address specific risks posed by individual chemicals, it is a comprehensive hazard information standard for nearly all chemicals in commerce.

Dose-Response Assessment

Carcinogens

OSHA's general procedures for dose-response assessment are similar to those of EPA and FDA, especially in the choice of data sets to use for quantitative assessments. However, OSHA probably uses a linear low-dose extrapolation model less often than is the case for other agencies. OSHA differs from the other federal regulatory agencies also in being less conservative in setting its target risk levels when conducting low-dose extrapolation. As previously noted, the main points of OSHA's risk assessments for regulatory purposes are to determine whether significant risks exist and to demonstrate in a broad sense the degree to which the standard would reduce significant risk. The specific choice of where to set

[9] "Occupational Exposure to 1,3-Butadiene" 61 FR 56746 (Nov. 4, 1996).

the standard is tempered by the statutory mandate that standards must be technologically and economically feasible.

Like other agencies, OSHA states that, all things being equal, epidemiological data are preferred over data from animal studies whenever good data on human cancer risks exist. More often than some other agencies regulating exposures to toxic substances, OSHA may have relevant human data on adverse health effects available for consideration in its risk assessments. However, the rulemaking examples we reviewed also illustrate that these epidemiological data may be considered inadequate for quantitative dose-response assessment, while animal data may provide more precise and useful dose-response information. In both the methylene chloride and 1,3-butadiene dose-response assessments, for example, OSHA had both epidemiological and animal data available, but based its quantitative estimates on data from rodent models. However, OSHA did use its analysis of the epidemiological data when examining the consistency of the results derived from animal studies.

When faced with the choice of several animal data sets, OSHA tends not to combine tumor sites but to choose the data set showing the highest sensitivity (i.e., most sensitive sex, species, and tumor site). The agency will, however, frequently present information from alternative data sets and analyses. The agency is likely to include benign tumors with the potential to progress to malignancy along with malignant tumors in the data set used for its quantitative assessments. OSHA cited the Office of Science and Technology Policy's views on chemical carcinogens in support of this practice, as well as noting that other federal agencies, including EPA and FDA, have also included benign responses in their assessments.

Because occupational exposures tend to be closer to the range of experimentally tested doses in animal studies, extrapolation may pose less of a challenge for OSHA than for other regulatory agencies. OSHA's preferred model for quantitative analysis of animal cancer dose-response data and for extrapolation of these data to low doses is the "multistage model," which is based on the biological assumption that carcinogens induce cancer through a series of independent ordered viable mutations, and that cancer develops through stages. Unlike EPA and FDA, however, OSHA tends to focus on the maximum likelihood estimate (MLE) of the fitted dose-response curve rather than on an upper bound, although the agency also provides estimates for the 95-percent upper confidence limit (UCL) of the dose-response function. This procedure generally leads to a less conservative risk estimate than the procedures used by EPA or FDA.

Like EPA and FDA, OSHA generally assumes no threshold for carcinogenesis. In contrast to the other agencies, OSHA's default dose-metric for interspecies extrapolation is body weight scaling (mg/kg/day – i.e., risks equivalent at equivalent body weights). According to OSHA, this default is used to be consistent with prior chemical risk assessments, but it also reflects a conscious policy decision that its methodology should not be overly conservative. OSHA says it may in the future move to ¾ -power scaling, as agreed to by EPA, FDA, and the Consumer Product Safety Commission some years ago. OSHA also says it is currently considering developing a different form of the multistage model, which will provide more stable MLE estimates than does the current form.

OSHA also considered data from physiologically based pharmacokinetic (PBPK) models in the risk assessment examples we reviewed.[10] PBPK models provide information on target organ dose by estimating the time distribution of a chemical or its metabolites through an exposed subject's system.[11] OSHA noted that PBPK modeling can be a useful tool for describing the distribution, metabolism, and elimination of a compound of interest under conditions of actual exposure and, if data are adequate, can allow extrapolation across dose levels, routes of exposure, and species. In particular, pharmacokinetic information is useful in modeling the relationship between administered doses and effective doses as a function of the exposure level.[12] However, PBPK models are complicated and require substantial data, which may not be available for most chemicals. OSHA pointed out in the methylene chloride rule that differences in the risk estimates from alternative assessments (including those submitted by outside parties) were not generally due to the dose-response model used, but to whether the risk assessor used pharmacokinetic modeling to

[10] Pharmacokinetics is the study of the absorption, distribution, metabolism, and elimination of chemicals in humans and animals. It is the basis for developing more realistic and accurate models of the movement and interactions of a chemical with blood, tissues, and organs once it enters the body, including consideration of the body's ability to repair damage caused by a chemical. PBPK models are based on the physiology of the exposed subjects, in contrast to more general compartmental pharmacokinetic models that do not necessarily represent effects on real anatomic regions/compartments of the body.

[11] Once in the body, a chemical may be chemically altered to form metabolites. Either the chemical itself or its metabolites may produce toxic effects. Therefore, both may need to be considered in assessing the potential harm associated with a given chemical.

[12] The administered dose is the amount of a substance given to an animal or human (e.g., through diet, drinking water, or ambient air). The effective dose is the amount that actually reaches a target organ or tissue.

estimate target tissue doses and what assumptions were used in that modeling.

In the methylene chloride standard, OSHA developed a set of 11 criteria to judge whether available data are adequate to permit the agency to rely on PBPK analysis in place of administered exposure levels when estimating human equivalent doses. Although it is beyond the scope of this appendix to provide a full technical explanation of the following criteria, they do illustrate the complex nature of PBPK analysis and, more generally, the types of issues that risk assessors consider in weighing the available data.

1. The predominant as well as all relevant minor metabolic pathways must be well described in several species, including humans.

2. The metabolism must be adequately modeled.

3. There must be strong empirical support for the putative mechanism of carcinogenesis.

4. The kinetics for the putative carcinogenic metabolic pathway must have been measured in test animals *in vivo* and *in vitro* and in corresponding human tissues at least *in vitro*.[13]

5. The putative carcinogenic metabolic pathway must contain metabolites that are plausible proximate carcinogens.

6. The contribution to carcinogenesis via other pathways must be adequately modeled or ruled out as a factor.

7. The dose surrogate in target tissues used in PBPK modeling must correlate with tumor responses experienced by test animals.

8. All biochemical parameters specific to the compound, such as blood:air partition coefficients, must have been experimentally and reproducibly measured. This must especially be true for those parameters to which the PBPK model is sensitive.

[13] The term *in vivo* refers to tests carried out within living organisms, while *in vitro* refers to tests outside the organism (e.g., using cells taken from an animal or human).

9. The model must adequately describe experimentally measured physiological and biochemical phenomena.

10. The PBPK models must have been validated with other data (including human data) that were not used to construct the models.

11. There must be sufficient data, especially data from a broadly representative sample of humans, to assess uncertainty and variability in the PBPK modeling.

In the 1,3-butadiene standard, which came out after the methylene chloride standard, OSHA used these same 11 criteria to judge the adequacy of the 1,3-butadiene PBPK models for dose-response assessment. In the butadiene case, the PBPK models did not meet all of these criteria.

For dose-response analyses from human cancer data, OSHA tends to use similar methodologies to the other regulatory agencies. Mostly these are simple linear models, such as relative risk models, and estimates of risk are based on the MLE.

Noncancer Effects

No specific approach or procedure for the assessment of noncancer effects was evident in the examples of OSHA rulemakings we reviewed. However, OSHA clearly considered a range of noncancer toxic effects in its analyses. In its rulemakings, OSHA focused on describing and analyzing a variety of relevant studies, case reports, and other information found in the scientific literature. Rhomberg noted that, in the past, OSHA used methods that were comparable to those of other agencies. However, the federal court in the *AFL-CIO v. OSHA* case questioned the use of standard safety factors, noting that "application of such factors without explaining the method by which they were determined… is clearly not permitted."[14]

OSHA has produced quantitative risk estimates for reproductive and developmental effects (glycol ethers, 1993), heart disease and asthma (environmental tobacco smoke, 1994), Hepatitis B virus infection (bloodborne pathogens, 1992), tuberculosis, and kidney toxicity from cadmium exposure. OSHA is currently working on quantitative risk assessments for such adverse health effects as cardiovascular disease mortality, neural effects, asthma, and respiratory tract irritation for a number of substances. OSHA states that new methodology has been used

[14] 965 F.2d at 978.

for these assessments, but review drafts were not yet ready and we cannot comment further.

Exposure Assessment

Under the OSH Act, OSHA has a relatively specific and narrow focus on exposure assessment. OSHA's primary focus is estimating the risk to workers exposed to an agent for a working lifetime. This risk is calculated in terms of a person exposed at a constant daily exposure level for 45 years at 5 days per workweek and 8 hours per workday. The goal is to set standards, in the form of permissible exposure limits (PELs), so workers would suffer no impairment during the course of their lifetime under a continuous exposure scenario. Although this is a hypothetical exposure scenario, Rhomberg observed that it is not conservative compared with the actual distribution of exposures in the workplace. He also noted that, in assessing the exposures and risks associated with the new proposed standard, OSHA assumes that the standard is applied to newly exposed workers who will work under the new standard for their entire working lives. No allowance is made for the fact that current workers may already have had exposures higher than the new standard.

Despite the primary focus on long-term working lifetime exposures, there may also be some risks posed by acute, short-term exposures. Therefore, although part of OSHA's risk assessment could focus on longer-term risks and deal with 8-hour time-weighted average (TWA) exposure, the agency's analysis may also cover short-term exposure effects. In the methylene chloride rule, for example, OSHA set the 8-hour TWA PEL primarily to reduce the risk of employees developing cancer, while the 15-minute short-term exposure limit (STEL) was primarily designed to protect against noncancer risks, such as negative effects on the central nervous system.

Finally, Rhomberg pointed out the following distinct features of occupational exposure assessments:

> Compared to environmental exposures, exposures in the workplace tend to be much better defined. The workplace is a confined setting within which practices and behaviors tend to be standardized. Exposure levels are often high enough to be easily measured, and many workplaces have ongoing monitoring of environmental levels of compounds.[15]

[15] Rhomberg (1996), p. 36.

Risk Assessment Assumptions and Methodological Choices

As previously noted, OSHA's risk assessment procedures, including its default assumptions and methodological preferences, tend to be established through the precedents of prior rulemakings. In contrast to EPA and FDA, OSHA also appears to choose somewhat less conservative options, even though the agency notes that Congress and the courts have permitted and even encouraged it to consider "conservative" responses to both uncertainty and human variability. The Supreme Court's Benzene decision, in particular, affirmed that "the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of over-protection rather than under protection."[16] On the other hand, OSHA explicitly stated in rulemakings that it takes various steps to be confident that its risk assessment methodology is not designed to be overly conservative (in the sense of erring on the side of overprotection). Although not intended to be comprehensive, table 8 illustrates some of the specific assumptions or methodological choices used by OSHA. It also illustrates the overt balancing of more and less conservative choices that characterizes OSHA's approach to risk assessment. The information presented in table 8 was taken primarily from OSHA risk assessment documents but also reflects additional comments provided by OSHA officials. (GAO notes and comments appear in parentheses.)

Table 8: OSHA Risk Assessment Assumptions and Methodological Choices

Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
1. Most things being equal, epidemiologic data are preferred to data from animal studies whenever good data on human risks exist.	Avoids the uncertainty of cross-species extrapolation. Also, most human studies on nondrug chemicals come from occupational exposures.	Choice of data set for quantitative cancer risk assessment (hazard identification and dose-response assessment)	(Not identified.)

[16] 448 U.S. at 656.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
2. It is reasonable to suspect that substances that cause cancer in multiple animal species and at multiple target organ sites would be carcinogenic to humans. Therefore, OSHA relies on well-conducted, high-quality animal bioassays as the primary basis for cancer hazard identification and often for quantitative risk assessment.	Virtually all of the toxic substances that have been demonstrated to be carcinogenic in humans are also carcinogenic in laboratory animals.	Choice of data set for qualitative and quantitative cancer risk assessment (hazard identification and dose-response assessment) –in the absence of sufficiently powerful negative epidemiological studies or mechanistic studies demonstrating that the purported carcinogenic mechanism of action of the substance is irrelevant to humans.	(Not specifically identified, but OSHA did note that it is possible that a substance may be carcinogenic in a laboratory species but not in humans. OSHA officials also pointed out that, as part of its risk assessment, OSHA examines all relevant toxicity data to determine the appropriateness of relying on extrapolation from animal studies.)
3. If human (epidemiological) data are equivocal, or the epidemiologic study is not sufficiently sensitive to identify an increased risk predicted by a well-conducted animal bioassay, it is necessary to consider the animal data to protect workers from significant risk.	To protect workers from significant risk.	Analysis of epidemiological and animal data for quantitative cancer risk assessment (hazard identification and dose-response assessment) –when animal studies indicate a positive response to a particular chemical and epidemiological studies of exposures to the same chemical fail to exhibit a statistically significant increase in risk.	(Not identified.)
4. In the absence of pharmacokinetic information satisfying OSHA's criteria for acceptance of PBPK models, OSHA relies on a default mg/kg/day species conversion factor.	(Not identified.)	Choice of animal-to-human dose equivalence for quantitative risk assessment (dose-response assessment).	(Not identified, but this is generally considered to be a conservative approach.)
5. OSHA uses site-specific tumor incidence, rather than pooled tumor response, in determining the dose-response function for a chemical agent. OSHA estimates excess risks to humans based on the most sensitive species-sex-tumor site.	(Not explicitly identified. Per comments from OSHA it reflects, in part, a policy choice to be conservative, but not overly conservative.)	Choice of data set for quantitative cancer risk assessment (dose-response assessment).	OSHA cited this as an instance where the agency does not use the most conservative approach.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
6. OSHA combines benign tumors with the potential to progress to malignancies with malignant tumors occurring in the same tissue and the same organ site.	Evidence suggests that such tumors should be interpreted as representing a potentially carcinogenic response. (In support of this position, OSHA cited the views of the Office of Science and Technology Policy on chemical carcinogenesis [citation provided]. OSHA also pointed out that other federal agencies—EPA, FDA, the Consumer Product Safety Commission, and the National Institute for Occupational Safety and Health—have also included benign responses in their assessments.)	Choice of data set for quantitative cancer risk assessment (dose-response assessment).	(Not specifically identified in the risk assessments we reviewed, but according to OSHA officials is almost always conservative.)
7. OSHA relies on low-dose extrapolation to estimate risks associated with exposure levels of interest; however, because occupational exposures are typically much higher than those encountered in the general environment, OSHA's risk assessments do not extrapolate as far beyond the range of observed toxicity as might be necessary to characterize environmental risks.	(Not explicitly identified, but the assumption that you can extrapolate low-dose effects from high-dose effects is a standard assumption of risk assessment.)	Dose-response assessment.	(Not identified.)

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
8. For low-dose animal-to-human cancer risk extrapolation, OSHA's preference is to use the maximum likelihood estimate (MLE) in the Crump-Howe reparameterization of the "multistage model." This model is based on the biological assumption that carcinogens induce cancer through a series of independent viable mutations in a series of stages, and that each mutation rate is linearly related to dose. The multistage model used by the agency also assumes no threshold for carcinogenesis.	OSHA stated that it believes that the multistage model conforms most closely to what is known about the etiology of cancer, including the fact that linear-at-low-dose behavior is expected for exogenous agents, which increase the risk of cancer already posed by similar "background" processes. OSHA noted that there is no evidence that the multistage model is biologically inappropriate, especially for genotoxic carcinogens, and that the overwhelming scientific consensus is that genotoxins follow low-dose linear functions. However, OSHA officials also pointed out that the Crump-Howe algorithm that OSHA uses can yield nonlinear models. OSHA's preference is consistent with the position of the Office of Science and Technology Policy, which recommended that "when data and information are limited, models or procedures that incorporate low-dose linearity are preferred when compatible with limited information" [citation provided].	Cancer dose-response assessment.	The multistage model is generally considered to be a conservative model because it is approximately linear at low doses and because it assumes no threshold for carcinogenesis, although there are other plausible models of carcinogenesis which are more conservative at low doses. (OSHA officials also pointed out that the algorithm that OSHA uses to compute MLE estimates is less conservative because it may lead to models that are sublinear at low doses.)
9. OSHA's default choice is to select the MLE of the parameterized dose-response function, rather than the upper 95-percent confidence limit.	In part, this appears to reflect a policy choice. OSHA cited this choice as one of the steps it has taken that make it fairly confident its risk assessment methodology is not designed to be overly "conservative," in the sense of erring on the side of overprotection.	Cancer dose-response assessment.	OSHA cited this as an instance where the agency does not use a conservative (or the most conservative) approach.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
10. For interspecies dose scaling, OSHA assumes that equivalent doses in mg/kg/day (body weight scaling) would lead to equivalent risks. (OSHA's Director of Health Standards noted that the agency might also move to consideration of ¾-power scaling, as agreed to by EPA, FDA, and the Consumer Product Safety Commission, or to develop a probability distribution for the power.) In addition, to convert mg/kg/day doses to parts per million (ppm), OSHA uses a human breathing rate of 9.6 m^3/workday and human body weight of 70 kg.	In its risk assessments, OSHA points out that there are several plausible options for extrapolating human risks from animal data via interspecies scaling factors [citations provided]. OSHA states that its selection of body weight scaling is one of the steps it takes that make the agency fairly confident that its risk assessment methodology is not "conservative" in the sense of erring on the side of overprotection. (No particular basis cited for using the specific breathing rate and body weight figures, just that they are OSHA's preferred values.)	During dose-response assessment, when estimating the equivalent human dose based upon an experimental dose in animals.	OSHA notes that the body weight extrapolation approach that it generally uses tends to be significantly less conservative than other plausible methodologies and most likely is less conservative even than the central tendency of the plausible values. The agency also notes that, across the series of plausible values, its body weight extrapolation approach is generally considered the least conservative, $(\text{body weight})^{2/3}$ [surface area scaling] the most conservative, and $(\text{body weight})^{3/4}$ the midpoint value.
11. OSHA assumes that workers will be exposed to a chemical at the maximum permissible level for 45 years. The standard values used for assessing exposures over a working lifetime are: a. 45 years per working lifetime, b. 5 workdays per week, and c. 8 hours per workday.	The focus on working lifetime exposure comes from the statutory mandate under the OSH Act to protect an employee "even if such employee has regular exposure to the hazard… for the period of his working life." The choice of 45 years is based on a worker beginning work at age 20 and retiring at age 65.	Exposure assessment.	OSHA notes that this reflects a "more conservative" choice.

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Assumption or methodological choice	Reason(s) for selection	When the assumption/choice would be applied (step in the risk assessment process or circumstances)	Likely effect on risk assessment results
12. The general boundary within which acceptable versus unacceptable risk falls is between an insignificant fatality risk of one in one billion (10^{-9}) and a significant risk of 1 in one thousand (10^{-3}). More explicitly, OSHA stated in one of its rulemakings that risks at or above 10^{-3} (1 per 1000) are always significant by any empirical, legal, or economic argument available.	The general boundary is directly attributed to the Supreme Court's 1980 Benzene decision.	Policy for evaluating "significant risk."	(No direct effect on the risk estimates, but this general policy does serve as an underlying focus in conducting risk assessments.)

Source: Compiled from GAO review of OSHA risk assessment documents and from additional comments provided by agency officials.

Risk Characterization

Although OSHA does not have written risk characterization policies, recent OSHA rulemakings showed that the agency emphasized (1) comprehensive characterizations of risk assessment results; (2) discussions of assumptions, limitations, and uncertainties; and (3) disclosure of the data and analytic methodologies on which the agency relied. Rhomberg noted that OSHA's usual practice is to present the results and methodological bases of outside parties' risk assessments for a chemical in addition to OSHA's own assessment, and to feature several possible bases for risk calculation in its characterization of risks. In checking examples of recent OSHA rulemakings, we also observed this emphasis on showing a range of alternative assessments, both those of external parties and OSHA's own sensitivity analyses.

At least three factors help to explain this proclivity to characterize risks using different data sets, assumptions, and analytical approaches, all of which are rooted in the statutory context for OSHA standards setting. First, the agency's statutory mandate, reinforced by the Supreme Court's Benzene decision, is that it must demonstrate "significant" risk from workplace exposure to a chemical with "substantial evidence." Second, the OSH Act directs OSHA to base health standards on the "best available

evidence" and consider the "latest scientific data." The third factor is that the standard selected will be limited by consideration of its technological and economic feasibility and cost effectiveness. Together, these provisions provide ample incentive to show that a compound presents a significant risk even when using a range of alternative estimates and scientific evidence. (This does not preclude the agency from focusing on one analysis as the most appropriate to support its final estimate of risk at a particular level of exposure.) The bottom line is that OSHA uses risk assessment to justify a standard by showing, in general, that significant risks exist and that reducing exposure as proposed in the agency's standard will reduce those risks.

In recent OSHA rulemakings, the agency devoted considerable effort to addressing uncertainty and variability in its risk estimates. Such efforts included performing sensitivity analyses, providing the results produced by alternative analyses and assumptions, and using techniques such as Monte Carlo and Bayesian statistical analyses. In its risk characterizations, OSHA provided both estimates of central tendency (such as the mean) and upper limits (such as the 95^{th} percentile of a distribution). In the methylene chloride rule, OSHA noted that, in its past rulemakings, it had frequently estimated carcinogenic potencies via the MLE of the multistage model parameters. However, in this particular rule it chose for its final risk estimate to couple one measure of central tendency (the MLE of the dose-response parameters) with a somewhat conservative measure of its PBPK output (the 95^{th} percentile of the distribution of human internal dose). OSHA concluded that this combination represented "a reasonable attempt to account for uncertainty and variability."

Chemical Risk Assessment at the Department of Transportation's Research and Special Programs Administration

The chemical risk assessments conducted by the Department of Transportation's (DOT) Research and Special Programs Administration (RSPA) focus primarily on acute (short-term) risks associated with potential accidents involving unintentional releases of hazardous materials (HAZMAT) during transportation.[1] As such, they are very different from risk assessments that focus on chronic health risks. According to agency officials, RSPA's assessments are done using a flexible, criteria-based system. RSPA's HAZMAT transportation safety program begins with a hazard analysis that results in material classification. There are international standards on the transportation and labeling of dangerous goods that classify the type of hazard associated with a given substance (e.g., whether it is flammable, explosive, or toxic) and the appropriate type of packaging. Once a hazard is classified, RSPA's analysis focuses on identifying the potential circumstances, probability, and consequences of unintentional releases of hazardous material during its transportation. DOT has written principles on how the results of its risk or safety assessments should be presented. Those principles emphasize transparency regarding the methods, data, and assumptions used for risk assessments and encourage DOT personnel to not only characterize the range and distribution of risk estimates, but also to put the risk estimates into a context understandable by the general public.

Context for RSPA Chemical Risk Assessment

According to DOT officials, chemical risks may be an element of almost any departmental risk assessment. For example, they said that one of the alternatives they explored regarding air bags involved potential exposure to chemicals used in the inflation mechanism. They also noted that Federal Aviation Administration (FAA) safety analyses include some elements related to potential exposures to the chemicals that are always found in aircraft mechanisms. However, DOT's risk assessment most commonly focus on chemical risks when considering the transportation of hazardous materials. Unintentional releases of hazardous materials during transportation, whether due to packaging leaks or transportation accidents, may pose risks to human health and safety, the environment, and property. The potential consequences of such incidents include deaths or

[1] DOT uses the term "risk assessment" narrowly to refer to risk characterization, specifically the determination of risk context and acceptability, often by comparison to other similar risks. However, to be consistent with the rest of this report, we are using the term in this appendix to refer to the entire process of identifying, analyzing, and characterizing risks.

injuries caused by an explosion, fire, or release of gases that are toxic when inhaled.

Under the Federal Hazardous Materials Transportation Act, as amended, the Secretary of Transportation has the regulatory authority to provide adequate protection against risks to life and property inherent in transporting hazardous materials in commerce.[2] DOT officials pointed out that, because this act tends to be more general than those relevant to other agencies' regulation of risks from chemicals, it gives DOT more flexibility to define what is "adequate" to address potential risks. The statute directs the DOT Secretary to designate a material or group or class of materials as hazardous when he or she decides that transporting the material in commerce in a particular amount and form may pose an unreasonable risk to health and safety or property. The Secretary is also directed to issue regulations for the safe transportation of such materials. The hazardous materials regulations apply to interstate, intrastate, and foreign transportation in commerce by aircraft, railcars, vessels (except most bulk carriage), and motor vehicles.

The Secretary has delegated authority for implementing these hazardous materials responsibilities to various components within DOT. In particular, RSPA issues the Hazardous Materials Regulations and carries out related regulatory functions, such as issuing, renewing, modifying, and terminating exemptions from the regulations. The Superfund Amendments and Reauthorization Act of 1986 mandated that RSPA also list and regulate under the Hazardous Materials Regulations all hazardous substances designated by EPA. According to DOT officials, RSPA conducts most of the department's risk assessments regarding the transportation of chemical hazardous materials. RSPA and the modal administrations in DOT—FAA, the United States Coast Guard, the Federal Motor Carrier Safety Administration, and the Federal Railroad Administration—share enforcement authority for hazardous materials transportation.

RSPA's Office of Hazardous Materials Safety (OHMS) has the primary responsibility for managing the risks of hazardous materials transportation within the boundaries of the United States, unless such materials are being transported via bulk marine mode (in which case the Coast Guard is responsible). Overall, OHMS notes that its Hazardous Materials Safety Program and resulting regulations (1) are risk based; (2) use data,

[2] 49 U.S.C. 5101 *et seq.*

information, and experience to define hazardous materials and manage the risk hazardous materials present in transportation; and (3) are prevention oriented. Therefore, the analysis of risk is an important element of OHMS' responsibilities. Within OHMS, the Office of Hazardous Materials Technology (OHMT) provides scientific, engineering, radiological, and risk analysis expertise.

Other entities may also be involved in conducting transportation-related chemical risk and safety assessments. For example, OHMS sponsored a quantitative threat assessment by the John A. Volpe National Transportation Systems Center (the Volpe Center), which is operated by RSPA, to determine the probability that a life-threatening incident would occur as a result of transporting hazardous materials in aircraft cargo compartments.[3] OHMS also sponsored a multiyear research effort by the Argonne National Laboratory to characterize the risk associated with transportation of selected hazardous materials on a national basis.[4]

One of the most distinctive aspects regarding the regulation of hazardous materials transportation is the role that is played by international agreements and definitions. Criteria for classifying and labeling dangerous chemicals being transported have been internationally harmonized through the United Nations Recommendations on the Transport of Dangerous Goods.[5] This UN classification system is internationally recognized, and RSPA has essentially adopted the UN recommendations into the domestic hazardous materials regulations. (A more detailed description of this classification system appears in the following section.)

[3] *Threat Assessment of Hazardous Materials Transportation in Aircraft Cargo Compartments*, U.S. Department of Transportation, Research and Special Programs Administration, John A. Volpe National Transportation Systems Center, Final Report (December 1999).

[4] *A National Risk Assessment for Selected Hazardous Materials Transportation*, Decision and Information Sciences Division, Argonne National Laboratory (December 2000). The Argonne National Laboratory is operated by the University of Chicago under contract for the U.S. Department of Energy.

[5] The United States and other countries are attempting to develop a Globally Harmonized System (GHS) for the classification and labeling of chemicals. However, while criteria have been internationally harmonized for purposes of transportation, harmonized requirements have not yet been established for purposes of environmental, worker, or consumer safety regulations. RSPA participates, along with other federal agencies, in these GHS activities.

Risk Assessment Procedures

Because of the particular regulatory context in which it operates—in particular, its focus on acute (short-term) risks associated with transportation accidents—RSPA does not follow the four-step risk assessment paradigm identified by NAS and used by EPA, FDA, and OSHA. However, RSPA's procedures do address similar generic questions, such as whether a particular material or activity poses a threat and the likelihood and consequences of potential accidents. The agency uses a criteria-based system to assess the hazards to human health and safety, property, and the environment that are associated with potential accidents during hazardous materials transportation. Chemicals are identified and classified as hazards according to a classification system in the Hazardous Materials Regulations that is largely harmonized with internationally recognized criteria. The risk analyses by RSPA then focus on assessing the potential circumstances under which exposure could occur during transportation, their causes, consequences, and probability of occurrence.

Guidance

The general risk assessment procedures applicable to RSPA are found within DOT-wide policies on conducting regulatory analyses and also in descriptive materials about the agency's Hazardous Materials Safety Program. DOT included general guidelines for conducting a risk assessment as part of its broader *Methods for Economic Assessment of Transportation Industry Regulations* (Office of the Assistant Secretary for Policy and International Affairs, June 1982). The DOT guidelines for risk assessment are grouped under three major topics:

- procedural guidelines that recommend formats for presentation of risk analyses, formats for conducting risk analyses, and reporting of assumptions and limits of analyses;
- methodology guidelines that discuss some of the more frequently used risk methods and their applicability; and
- data guidelines that discuss data sources, collection and presentation of data, and raw and derived statistics.

The primary focus of the DOT-wide risk assessment methodology and guidelines is on estimating the risk reduction attributable to proposed transportation safety regulations. DOT's guidelines are intended to be applicable to risk assessment of hazardous material transport by any mode as well as assessment of other types of transportation risk. However, DOT stated that the guidelines are not intended to be a "cookbook," or a prescriptive methodology, specifying each step in a risk assessment. DOT

pointed out in the guidelines that such an approach is not desirable, because there is no single "correct" set of methods for assessing transportation risk.

In addition to the DOT-wide guidelines, RSPA has produced written materials specifically on the Hazardous Materials Safety Program. These materials describe the role of risk assessment in the management of risks associated with transportation of hazardous materials and the general process used for analysis of risks, and they define risk assessment and management terms for purposes of hazardous materials safety.[6] There also are a number of general guidance documents and reports on various aspects of hazardous materials transportation safety that provide additional insights into the identification and assessment of risks.

Risk Assessment Approach

RSPA does not apply the same NAS four-step paradigm for risk assessment as generally used by EPA, FDA, and OSHA. According to RSPA officials, the main reason for this difference between their risk assessments and most of those conducted by the other three agencies is the focus of RSPA's assessments. RSPA's concerns relative to hazardous materials transportation are primarily directed at short-term or acute health risks due to relatively high exposures from the unintentional release of hazardous materials. The officials said that, in contrast, the four basic steps of the NAS paradigm were intended to focus on chronic health risks due to long-term, low-level background chemical exposure.[7] The main exceptions to this difference in general risk assessment procedures occur when other agencies' assessments are similarly directed at risks associated with unintentional releases of chemicals. In particular, RSPA officials said that there are parallels between their risk assessment and management efforts and those of EPA and OSHA programs that are directed at chemical accidents. (See, for example, the description of the risk assessment procedures for EPA's Chemical Emergency Preparedness and Prevention Office in app. II.)

[6] DOT's definitions sometimes vary from the definitions of those terms in other risk assessment settings. Items in the glossary of this report identify some of these different definitions.

[7] Note, however, that the general risk assessment procedures of the other three agencies cover both chronic and acute risks.

In sharp contrast to most of the risk assessment procedures we described for EPA, FDA, and OSHA, toxicity is simply one of several potentially dangerous properties of a hazardous material of concern to RSPA. Where toxicity is a factor, RSPA's risk assessments tend to center on exposure levels that pose an immediate health hazard. This focus is reflected in the types of chemical toxicity information that RSPA helps develop. For example, RSPA actively participates on a National Advisory Committee developing Acute Exposure Guideline Levels for chemicals. In specific cases where chronic toxicity or environmental values play a role in RSPA analyses, agency officials said that they rely on what EPA, FDA, OSHA, and other agencies have developed.

Despite such differences, RSPA's risk assessments address similar basic issues as the chemical risk assessments of the other three agencies (e.g., whether a particular material or activity poses a threat and the severity and likelihood of potential exposures). The DOT-wide risk assessment guidelines primarily discuss "consequence" and "probability" analyses, but also describe a preliminary step for defining scenarios of concern (essentially part of a hazard identification step) and a final step to summarize results and conclusions from the preceding analyses (essentially a risk characterization). The Hazardous Materials Safety Program materials outline a similar risk assessment process that progresses from the identification of hazards to an evaluation of incident causes, frequencies, and consequences.

Identifying Hazards

RSPA begins with a hazard analysis that results in material classification. In RSPA risk assessments, hazardous materials are chemical, radioactive, or infectious substances or articles containing hazardous materials that can pose a threat to public safety or the environment during transport. Hazardous materials pose this threat through chemical, physical, nuclear, or infectious properties that can make them dangerous to transport workers or the public. For example, RSPA is concerned with the potential for the unintentional release of hazardous materials to lead to adverse outcomes such as explosions, fires, or severely enhanced fires that can cause deaths, injuries, or property damage. The agency is also concerned with the potential toxic, corrosive, or infectious effects of released materials on humans and the environment.

According to DOT officials, their hazard classification approach is a criteria-based system that provides them considerable flexibility in their analysis and regulation of potential hazards. They noted that their criteria are geared more toward the hazard a material may pose in an accident

scenario than toward a chronic health risk. The Director of the Office of Hazardous Materials Technology characterized this hazard classification approach as a more open system than used in other agencies (e.g., EPA). He explained that, in this system, any new chemical or substance that fits within RSPA's matrix of hazard criteria falls under the hazardous materials transportation regulations.

Hazard identification for these assessments is based largely on international agreements regarding transportation of dangerous goods. Of particular importance, there is an internationally recognized system for the classification, identification, and ranking of all types of hazardous materials that was created by the UN Committee of Experts on the Transport of Dangerous Goods. This system is revised biennially and published as the "United Nations Recommendations on the Transport of Dangerous Goods." Under this classification system, all hazardous materials are divided into nine general classes according to physical, chemical, and nuclear properties. The system also specifies subdivisions and packing group designations (that indicate a relative level of hazard) for some classes. (See table 9.)

Table 9: UN Classification System for Transport of Dangerous Goods

Hazard class	Description	Subdivisions specified	Packaging performance requirements specified
1	Explosives and pyrotechnics	X	
2	Compressed and liquefied gases	X	
3	Flammable liquids		X
4	Flammable solids (including self-reactive liquids)	X	X
5	Oxidizers and peroxides	X	X
6	Toxic (poisonous) and infectious materials	X	X
7	Radioactive materials		
8	Corrosive materials (acidic or basic)		X
9	Miscellaneous dangerous substances and articles		
Packing groups			
1	Great danger		
2	Medium danger		
3	Minor danger		

Source: Research and Special Programs Administration, Department of Transportation.

These are broad categories that may include large numbers of diverse materials. For example, the air cargo threat assessment noted that there were 535 different flammable liquid entries in the hazardous materials table and more than 700 toxic material entries. Because there are hazardous materials with multiple dangerous properties, these classes and subdivisions are not mutually exclusive. Compressed or liquefied gases, for example, also may be toxic or flammable. The UN Committee of Experts created more than 3,400 possible identification numbers, proper shipping descriptions, and hazard classes to be assigned to various hazardous material compounds, mixtures, solutions, and devices. There are also generic "not otherwise specified" identification numbers and shipping descriptions that allow the material to be classed by its defined properties.

RSPA uses essentially the same framework as the UN recommendations for the hazard classes and packing requirements of its Hazardous Materials Regulations. Table 10 shows the hazard classification system in the regulations.

Table 10: Hazard Classification System of RSPA's Hazardous Materials Regulations

Class/division number	Description
None	Forbidden materials[a]
None	Forbidden explosives[b]
Class 1	Explosives
• Division 1.1	• Explosives with a mass explosion hazard
• Division 1.2	• Explosives with a projection hazard
• Division 1.3	• Explosives with predominantly a fire hazard
• Division 1.4	• Explosives with no significant blast hazard
• Division 1.5	• Very insensitive explosives; blasting agents
• Division 1.6	• Extremely insensitive detonating articles
Class 2	Gases
• Division 2.1	• Flammable gas
• Division 2.2	• Nonflammable compressed gas
• Division 2.3	• Poisonous (toxic by inhalation) gas
Class 3	Flammable and combustible liquid
Class 4	Flammable solids; spontaneously combustible materials; and dangerous when wet materials
• Division 4.1	• Flammable solid
• Division 4.2	• Spontaneously combustible material
• Division 4.3	• Dangerous when wet material

(Continued From Previous Page)

Class/division number	Description
Class 5 • Division 5.1 • Division 5.2	Oxidizers and organic peroxides • Oxidizer • Organic peroxide
Class 6 • Division 6.1 • Division 6.2	Poisonous (toxic) materials and infectious substances • Poisonous (toxic) materials • Infectious substance (etiologic agent)
Class 7	Radioactive material
Class 8	Corrosive material
Class 9	Miscellaneous hazardous material
None	Other regulated material

[a]49 CFR Section 173.21 defines the materials that shall not be offered for transportation or transported.

[b]49 CFR Section 173.54 defines the explosives that shall not be offered for transportation or transported.

Source: 49 CFR section 173.2.

The classification system in these regulations can be very detailed for some subjects. For example, the regulations specifically identify the types of toxicity tests and data that should be used to determine whether something would be classified as poisonous material (class 6, division 6.1). The regulations define poisonous material as a material, other than a gas, which is known to be so toxic to humans as to afford a hazard to health during transportation, or which, in the absence of adequate data on human toxicity,

- is presumed to be toxic to humans because it falls within one of several specified categories for oral, dermal, or inhalation toxicity when tested on laboratory animals; or
- is an irritating material, with properties similar to tear gas, which causes extreme irritation, especially in confined spaces.

Of particular relevance to comparisons with chemical risk assessments of other agencies, the regulations contain precise definitions of what constitutes oral, dermal, or inhalation toxicity for purposes of the Hazardous Materials Regulations. For example, one threshold for inhalation toxicity is defined as a dust or mist with an LC_{50} for acute toxicity on inhalation of not more than 10 mg per liter of air.[8] (A different definition applies to the inhalation toxicity of a vapor.) The regulations also address other testing requirements and conversion factors. The regulations state that, whenever possible, animal test data that have been reported in the chemical literature should be used.

The Hazardous Materials Regulations include an extensive Hazardous Material Table with itemized information about specific hazardous materials. The number of HAZMAT table entries corresponds closely with the number created by the UN. RSPA officials noted that the number of specific chemicals covered by the regulations is many multiples of the more than 3,400 entries, though, because of the generic nature of the "not otherwise specified" descriptions. The table includes, but is not limited to, information such as the material's description, hazard class or division, identification number, packing group, label codes, limits to the quantity of the material permitted in a single package, and special provisions concerning its transportation. Allyl chloride, for example, is identified as a class 3 material (flammable and combustible liquid), is in packing group I (indicating great danger), is forbidden on passenger aircraft and rail, and has two special provisions regarding the tanks used for transporting this substance. A material that meets the definition of more than one hazard class or division, but is not specifically listed in the table, is to be classed according to the highest applicable hazard class or division according to a descending order of hazard. For example, the division of poisonous gases is ranked as a greater hazard than the division of flammable gases.

According to OHMS, the process of classifying a material in accordance with these hazard classes and packing groups is itself a form of hazard analysis. Another important feature of this process is that the regulations require the shipper to communicate the material's hazards through the use of the hazard class, packing group, and proper shipping name on the shipping paper and the use of labels on packages and placards on the

[8] In this case, LC_{50} for acute toxicity on inhalation means that concentration of dust or mist which, administered by continuous inhalation for 1 hour to both male and female young adult albino rats, causes death within 14 days in half of the animals tested.

transport vehicle. Therefore, the shipping paper, labels, and placards communicate the most significant findings of the shipper's hazard analysis to other parties. This communication aspect is particularly important in emergency response situations if an accident occurs during transport of these materials.

The classification system, by itself, is not sufficient for all risk assessment purposes. For example, RSPA and OHMS still need to identify potential scenarios in which transportation accidents, spills, and leaks could occur. As evidenced by the air cargo threat assessment, such scenarios include the possibility that hazardous materials might be transported in a manner not in compliance with current regulations.[9] Also, as emphasized in a November 2000 report for RSPA, the hazardous materials transport system is highly heterogeneous and complex.[10] The report pointed out that this system involves not only many different materials posing a variety of hazards (as reflected in the classification system outlined in table 9) but also:

- a chain of events involving multiple players having different roles in the process of moving hazardous materials (such as shippers, carriers, packaging manufacturers, freight forwarders, and receivers of shipments) and the possibility of multiple handoffs of a material from one party to another during transport;
- several different modes of transport (principally highway, rail, waterway, and air), with some shipments that switch from one mode to another during transit; and
- multiple possible routes of transit.

[9] The threat assessment project was, in fact, initiated following the crash of ValuJet Flight 592 near Miami, FL in May 1996, which had been linked to hazardous material devices (chemical oxygen generators) shipped in violation of DOT regulations.

[10] "Risk Management Framework for Hazardous Materials Transportation," prepared by ICF Consulting for the U.S. Department of Transportation, Research and Special Programs Administration (Nov. 1, 2000). RSPA officials noted that this framework provides a structure for their efforts and serves as a tool for all parties involved in hazardous materials transportation to consider in fostering continuous safety improvement.

All of these complex features might need to be considered in identifying hazard scenarios. However, in identifying (and analyzing) potential hazard scenarios, RSPA and OHMS benefit from being able to use data, information, and experience on hazardous materials transportation incidents. For example, risk assessors can review data from sources such as the DOT Hazardous Materials Information System (HMIS) that catalogues transportation-related incidents that involve a release of hazardous materials. An OHMS official pointed out that the agency also uses fairly sophisticated models in analyzing various scenarios. He said that such models were used, for example, to provide a scientific basis for determining evacuation zones when developing the *2000 Emergency Response Guidebook*.[11]

Analyzing the Consequences and Probabilities of Risks

In contrast to the other agencies covered in this report, determining the toxicity of a particular chemical (dose-response assessment) is not a central focus of risk assessment in RSPA and OHMS. Toxicity is only one of many risk factors under consideration (and should already be addressed through the hazard classification system). Instead, the primary focus of analysis is on the potential for hazardous materials to (1) spill or leak while in transit or (2) cause, contribute to, or multiply the consequences of a transportation-related accident. Analysis regarding the first item is primarily concerned with the packaging and containers used for transportation of hazardous materials, while analysis of the second item also considers other elements, such as the modes and routes of transportation for these materials. As the DOT risk assessment guidelines state, "Hazardous materials accidents generally are transportation accidents in which hazardous materials happen to be present."

DOT documents use a variety of terms to describe and refer to the analysis of hazards or risks of concern to the department and its component offices (e.g., hazard analysis, risk analysis, threat assessment). However, the core of the analysis remains the same—an evaluation of the causes,

[11] The *2000 Emergency Response Guidebook* was developed jointly by DOT, Transport Canada, and the Secretariat of Communications and Transportation of Mexico. It is intended primarily to guide firefighters, police, and other emergency personnel who may be the first to arrive at the scene of a transportation incident involving a hazardous material in (1) quickly identifying the specific or generic classification of the material(s) involved in the incident, and (2) protecting themselves and the general public during the initial response phase of the incident. According to RSPA, the 2000 revision of this guidebook was based on risk principles and analyses, and the technical basis and derivation of the values in the guidebook's Table of Initial Isolation and Protective Action Distances are available on the RSPA website.

consequences, and likelihood of transportation incidents involving hazardous materials. The general model in DOT's guidelines for risk assessment of transportation activities or operations partitions the analysis of risk into two main parts:

- prediction of possible consequences in terms of loss from accidents (or, more broadly, incidents) while transporting materials in a specified way; and
- estimation of the probabilities or frequencies of occurrence of the consequences of such accidents (e.g., the likelihood or expected number of accidents occurring that would result in the above loss).

For purposes of estimating the risk reduction attributable to transportation safety regulations, the expected loss or "risk" is computed by summing the products of each possible loss multiplied by its probability. (In other words, risk in this context is the probability-weighted average loss.)

According to DOT definitions, consequence analysis is the evaluation of the severity and magnitude of impacts associated with the occurrence of postulated accident scenarios. For purposes of analysis, the DOT guidelines recommend partitioning this evaluation into three segments: (1) initiating events (i.e., causes of an accident that can result in loss), (2) effects (i.e., the possible mechanisms by which an initiating event might result in injury or damage); and (3) consequences (i.e., the loss of life, injuries, property damage, or other losses expected from the effects). The evaluation of consequences reflects many factors, including the characteristics of the agent involved, the type of packaging or container used, the amount of material being transported, and the particular modes and routes of transportation (which also affect the extent of potential exposure by the public and environment). DOT defines probability analysis as the evaluation of the likelihood of individual accident scenarios and outcomes of adverse events. The likelihood of a particular hazard might be expressed either as a frequency or probability.

The analyses of consequences and probabilities are based on a variety of data sources, including, to the extent possible, "experience" data. Among the sources of information identified in OHMS materials to address consequences and probabilities are:

- data from the Hazardous Materials Information System (HMIS);
- commodity flow surveys;
- chemical substance manufacturing, use, and transportation studies;

- special analyses (such as the National Transportation Risk Analysis and Air Cargo reports mentioned earlier in this appendix, as well as shipment counts); and
- public comments on rulemakings.

Such sources can provide valuable information for risk assessment in general and the statistical analysis of hazardous material transportation incidents in particular. The HMIS database provides a good illustration of the types of baseline data available. This database provides incident counts according to time, transportation phase (i.e., en route from origin to destination, loading or unloading, and temporary storage), and transportation mode (e.g., air, highway, and rail). For each incident, the database includes information on the hazardous materials involved, including the name of the chemical shipped, container type and capacity, number of containers shipped, number of containers that fail, and the amount of material released. The database also contains information concerning the occurrence of fire, explosion, water immersion, environmental damage, and the numbers of deaths, major and minor injuries, and persons evacuated.

However, because DOT's risk assessments are often used to estimate the "risk impact" of proposed regulations, the DOT guidelines caution that lack of directly applicable experience data for assessing the impacts is probably the rule rather than the exception. This is because the controls provided by the proposed regulations constitute changes from present conditions, and experience data, by definition, relate to present conditions. The guidelines also emphasize that, to evaluate the impact on risk of a proposed regulation or its alternatives, it is necessary to perform a "with and without" type of assessment, considering the potential effects on any or all of the elements of the risk model.

As was the case with the classification of hazardous materials and packaging, the agency may employ criteria-based classifications of the consequences of potential adverse events and their likelihood of occurrence. A 1995 guidance document illustrates how consequence and frequency categories were combined into a "risk assessment matrix" to assist decision makers in their risk management decisions.[12] (See table 11 below.)

Table 11: Example of a Hazardous Materials Risk Assessment Matrix

	Consequence of occurrence categories				
Frequency of occurrence categories	**Catastrophic**	**Critical**	**Marginal**	**Minor**	**Negligible**
Frequent	U	U	U	C-MDR	A-MRR
Probable	U	U	C-MDR	A-MRR	A-MRR
Occasional	U	C-MDR	A-MRR	A-MRR	A
Remote	C-MDR	A-MRR	A-MRR	A	A
Improbable	A-MRR	A-MRR	A	A	A

Risk index:

U - Unacceptable

C-MDR - Conditional –management decision required

A-MRR - Acceptable –management review required

A - Acceptable

Source: Adapted from "Procedure for Removal of Nonconforming Hazardous Materials Packagings from Service, 7-13-95," Office of Hazardous Materials Safety.

[12] In a nonchemical risk assessment context, DOT's Federal Transit Administration (FTA) and the American Public Transit Association recommend the use of very similar matrices for analysis of rail systems' safety. See FTA's *State Safety Oversight*, Issue 6 (Fall 1999).

As was the case with the three other agencies covered by our review, some of the chemical risk assessments produced by or for DOT have begun using more sophisticated methods and models. For example, the Director of OHMT characterized the National Transportation Risk Assessment study prepared for OHMS by the Argonne National Laboratory as using state-of-the-art risk assessment techniques to characterize risks associated with the transportation of selected hazardous materials on a national basis. The consequence assessments in this study employed the Chemical Accident Statistical Risk Assessment Model that predicts distributions of hazard zones (i.e., areas in which a threshold chemical concentration is exceeded) resulting from hazardous material release.[13] That model, in turn, reflected the input of other physical models on subjects such as hazardous material release rates of toxic-by-inhalation materials. The Director noted that his office believed this study to be the first comprehensive application of these techniques in this arena for this purpose.

Risk Assessment Assumptions and Methodological Choices

Although generally very structured and criteria based, RSPA's risk assessments for hazardous materials transportation also use assumptions. DOT-wide guidance documents provide a general framework for the use of assumptions. In general, DOT guidance recognizes that assumptions may be made when data are lacking or uncertain, or when it is necessary to limit the scope of an analysis. However, the assumptions, while not empirically verifiable, are supposed to be reasonable, logically credible, and supportable in comparison with alternative assumptions. The DOT risk assessment methodology guidance specifically states that every assessment should include a list of the major assumptions, conditions, and limitations of the risk analysis, as well as the reasons why the assumptions were made.

As noted earlier in this appendix, RSPA has access to a number of sources of directly relevant data and statistics on the transportation of hazardous materials. However, there are limitations to these systems and data. For example, the authors of the national transportation risk assessment for selected hazardous materials cautioned that the information in DOT's data systems was not always sufficient or detailed enough to directly support a quantitative risk assessment. For example, incidents involving most

[13] Rather than specifying a deterministic measure of risk, this model determines the distribution of possible outcomes, allowing the probability of a particular consequence to be identified within the limits of the statistical data used.

hazardous materials (other than gasoline-truck accidents) typically occur too infrequently to provide statistically reliable data for directly projecting future risks. In his introduction to the study, the Director of OHMT also stated that the quantitative results of this study should be used with caution. Specifically, he noted, "While the model of the hazardous materials transportation system employed in this study is sophisticated, the accuracy of the data used in the model is often less precise. Estimates, assumptions, and aggregate numbers have been used in many cases."

Some of the topics that might require assumptions or choices during a hazardous materials transportation assessment include:

- the probability of the release of a hazardous material, depending on the nature of the accident, type of material being transported, and the containers used;
- the amount of material released in an accident, depending again on factors such as the severity of the accident, nature of the material, and type of container, but also depending on assumptions about the size of holes in containers;
- commodity flows of the materials (e.g., modes of transportation used, classes of rail tracks, types of highways, routing through urban and rural areas and related population density);
- the dispersion of released hazardous material, including assumptions about climate and meteorological conditions and the type of surface that a liquid might "pool" on if spilled;
- the probability of a fire or explosion being ignited (both as a consequence of a release or as a cause of a release); and
- the extent to which humans potentially exposed to released materials would be sheltered or protected (both within a given mode of transportation, such as an aircraft, or external to the carrier).

In addition to these topics, RSPA sometimes uses a factor to adjust data in the HMIS database to address underreporting. However, RSPA officials noted that, for certain purposes, it might be inappropriate to extrapolate information in the database.

Although assumptions may be needed in RSPA assessments, RSPA officials said that they do not have default assumptions for their risk assessments. According to the officials, assumptions must be developed and described as part of each risk assessment and are specific to the risk assessment. RSPA officials also noted that they do not use "safety factors" in risk assessments, but rather base their assessments on expected levels or

ranges of performance. Therefore, unlike in the appendices on EPA, FDA, and OSHA, we have not included a table in this DOT appendix to identify major default choices, the reasons for their selection, when they would be used in the process, and their likely effects on risk assessment results. However, with regard to some of the case-specific assumptions or choices we identified during our review, we did observe that DOT's assessments typically discussed the reasons for particular choices (as with the other agencies, often citing an interpretation of related research studies). In some instances, information was also provided on the likely effect (e.g., that a particular value represented a conservative estimate or an upper limit) or level of uncertainty (e.g., that a particular parameter value might be high by a factor of 3 to 10 times the results from another study) associated with choices made by the analysts.

Risk Characterization

DOT has explicit, written principles regarding how the results of its risk or safety assessments should be presented. The department's policies emphasize the principle of transparency and encourage agency personnel to not only characterize the range and distribution of risk assessment estimates, but also to put risk estimates into a context understandable by the general public. For example, DOT's "risk assessment principles" state that the risk assessment should:

- make available to the public data and analytic methodology on which the agency relied in order to permit interested entities to replicate and comment on the agency's assessment;
- state explicitly the scientific basis for the significant assumptions, models, and inferences underlying the risk assessment, and explain the rationale for these judgments and their influence on the risk assessment;
- provide the range and distribution of risks for both the full population at risk and for highly exposed or sensitive subpopulations, and encompass all appropriate risks, such as acute and chronic risks, and cancer and noncancer risks, to health, safety, and the environment;
- place the nature and magnitude of risks being analyzed in context, including appropriate comparisons with other risks that are regulated by the agency as well as risks that are familiar to, and routinely encountered by, the general public, taking into account, for example, public attitudes with respect to voluntary versus involuntary risks, well-understood versus newly discovered risks, and reversible versus irreversible risks; and

- use peer review where there are issues with respect to which there is significant scientific dispute to ensure that the highest professional standards are maintained.

The DOT risk assessment guidelines also state that every risk analysis should present information on (1) quantitative estimates of risk (over the entire range of plausible values of the developed variables, and with a "base case" loss to provide a point of reference); (2) insights gained from performing the analysis into the factors that most affect risk assessment results; and (3) assumptions, conditions, and limitations of the analysis. With regard to the third item, the guidelines specifically state that reasons why the assumptions were made, and why the limitations of the analysis do not significantly impact the risk estimate, should be provided. The guidelines also suggest two methods for treating uncertainty in a risk analysis:

- sensitivity analysis (DOT's preferred method for treating and reporting the impact of uncertainty), which should be conducted for each scenario in a risk analysis; and
- bounding analysis involving error propagation (requiring that each model parameter be expressed as a distribution, or at least a variance, to trace the implication of uncertainty for the risk estimate).

Glossary

Acceptable daily intake (ADI)	The maximum dose of a hazardous substance that can be consumed daily without causing adverse health effects over a lifetime.
Acute effect	An effect that results from a brief exposure or shortly after an acute exposure (possibly at high levels) of duration measured in minutes, hours, or days.
Additive dose-response model	A dose-response model in which the health effects attributable to exposure to particular levels of two or more risk agents are equal to the sum of the responses predicted for each agent alone.
Aggregate risk	The risk resulting from the combined exposure of an individual or defined population to a single agent or stressor via all relevant routes, pathways, and sources.
Ambient concentration	The average amount of a substance in a particular environmental medium, such as air or water.
Ambient water quality criteria (AWQC)	Numeric values limiting the amount of chemicals present in our nation's waters. Developed under section 304(a) of the Clean Water Act (CWA) and periodically updated, they are determined by assessing the relationship between pollutants and their effect on human health and the environment. These recommended criteria provide guidance for states and tribes in adopting water quality standards under section 303(c) of the CWA and to ultimately provide a basis for controlling discharges or releases of pollutants.
Benchmark dose	An exposure level that corresponds to a statistical lower bound on a standard probability of an effect, such as 10 percent of people affected.
Bioaccumulation factor (BAF)	Bioaccumulation is a process whereby the concentration of certain substances in organisms increases as the organisms breathe contaminated air, drink contaminated water, or eat contaminated food. The BAF is the

	ratio of a substances' concentration in an organism's tissue to its concentration in the medium where the organism lives. BAFs measure a chemical's potential to accumulate in tissue through exposure to both food and water.
Bioassay	The use of living organisms to measure the effect of a risk agent or condition—for example, a test for carcinogenicity in laboratory animals that includes near-lifelong exposure to the agent under test. Used interchangeably with *animal test*.
Biologically based dose response model	A model that describes biological processes at the cellular and molecular level linking the target organ dose to the adverse effect.
Cancer	A group of diseases characterized by abnormal, disorderly, and potentially unlimited new tissue growth.
Carcinogen	Any chemical or physical agent possessing the ability to induce cancer in living organisms.
Chronic health effects	Diseases occurring as a result of repeated or persistent exposures.
Chronic exposure	An exposure (usually of low concentration) of long duration, e.g., months or years.
Consequence	The direct effect of an event, incident, or accident. It is expressed as a health effect (e.g., death, injury, exposure), property loss, environmental effect, evacuation, or quantity spilled.
Contaminant(s)	Chemicals, microorganisms, or radiation found in air, soil, water, or food that are not normally constituents of these environmental media.

Cumulative risk	The combined risk from aggregate exposures to multiple agents or stressors.
Dose	The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. A **potential dose** is the amount ingested, inhaled, or applied to the skin. An **applied dose** is the amount presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism). An **absorbed dose** is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of the skin, lung, and digestive tract) through uptake processes. An **internal dose** denotes the amount absorbed without respect to specific absorption barriers or exchange boundaries. A **delivered** or **biologically effective dose** is the amount of the chemical available for interaction by any particular organ or cell.
Dose-response assessment	The determination of the relationship between the magnitude of administered, applied, or internal dose and a specified biological response.
Dose-response relationship	The relationship between exposure level and the incidence of adverse effects.
Ecological risk assessment	A process used to estimate the likelihood of adverse effects on plants or animals from exposure to stressors, such as chemicals or the draining of wetlands. The process includes problem formulation, characterization of exposure, characterization of ecological effects, and risk characterization.
Effluent	Treated or untreated waste material discharged into the environment. Generally refers to wastes discharged to surface waters.
Emission	Pollution discharged into the atmosphere from smokestacks, other vents, and surface areas of commercial or industrial facilities; residential chimneys; and motor vehicle, locomotive, or aircraft exhausts.

Environmental fate	The distribution and transformation of a chemical from its first release until its ultimate removal from or recycling through the environment.
Epidemiology	The study of diseases as they affect populations, including the distribution of disease, or other health-related states and events in human population; the factors (e.g., age, sex, occupation, economic status) that influence this distribution; and the application of this study to assess and control health risk. It involves investigating the causes and risk factors of disease and injury in populations and the potential to reduce such disease burdens.
Exposure	Contact of a chemical, physical, or biological agent with the outer boundary of an organism. Exposure is quantified as the concentration of the agent in the medium over time.
Exposure assessment	The process of developing a description of the relevant conditions and characteristics of human and other exposures to risk agents produced or released by a specified source of risk. This usually involves the determination or estimation of the magnitude, frequency, duration, and route of exposure.
Exposure pathway(s)	The physical course or means by which risk agents are transmitted—e.g., the route by which a given population, individual, species, or setting is exposed to a toxic substance (e.g., via drinking water, air, or dermal contact).
Exposure route	The way an environmental agent enters an organism (e.g., ingestion, inhalation, or dermal absorption).
Extrapolation	Prediction of the value of a variable outside the range of observation. This involves making inferences about the unknown by projecting or extending known information, using models and assumptions.
Genotoxic	Capable of causing heritable changes or damage leading to heritable changes in genetic material (i.e., altering the structure of DNA). A

	genotoxic carcinogen is one that initiates cancer through a direct effect on genetic material.
Hazard	A (potential) source of risk that does not necessarily produce risk. A hazard is the inherent characteristic of a material, condition, or activity that has the potential to cause harm to people, property, or the environment and produces risk only if an exposure pathway exists and if exposures create the possibility of adverse consequences.
Hazard analysis	The identification of material properties, system elements, or events that lead to harm or loss. The term hazard analysis may also include evaluation of consequences from an event or incident.
Incidence	The rate at which an event occurs. In toxicology, the number of new cases of a disease within a specified period of time, often expressed per 100,000 individuals per year.
Interspecies extrapolation	The act of applying a set of data or an individual test result from one species, under certain conditions and subject to particular dose levels of a toxic substance and application method, to another population of a different species under perhaps different conditions, dose levels, and application method.
LC_{50}	The concentration of a substance in air that when administered by inhalation to all animals in a test (over a specified time period) is lethal to 50 percent of the animals.
LD_{50}	The dose that when administered to all animals in a test (over a specified time period) is lethal to 50 percent of the animals.
Likelihood	Expressed as either a frequency or a probability. Frequency is a measure of the rate at which events occur over time (e.g., events per year, incidents per year, deaths per year). Probability is a measure of the rate of a possible

	event expressed as a fraction of the total number of events (e.g. 1/1,000,000).
Lowest effective dose (LED)	The lowest dose of a chemical that produced a specified level of an adverse effect when it was administered to animals in a toxicity study. For example, the LED_{10} is the lowest effective dose that produced an effect in 10 percent of the exposed animals.
Lowest observed adverse effect level (LOAEL)	The lowest exposure at which there is a statistically or biologically significant increase in the frequency of an adverse effect when compared with a control group.
Margin of exposure	A ratio defined by EPA as a dose derived from a tumor bioassay, epidemiologic study, or biologic marker study, such as the dose associated with a 10-percent response rate, divided by an actual or projected human exposure.
Mechanism of action/mode of action	The **mechanism of action** is the complete sequence of biological events that must occur to produce the toxic effect. The **mode of action** is a less-detailed description of the mechanism of action in which some but not all of the sequence of biological events leading to a toxic effect is known.
Monte Carlo analysis	The computation of a probability distribution over consequences by means of a random sampling method analogous to the game of roulette. Combinations of events and outcomes that yield possible consequences are randomly selected according to a specified probability distribution. The resulting consequences are counted and used to estimate other probability distributions.
Multistage models	Dose-response models that assume a given number of biological stages occur following exposure to a risk agent (e.g., metabolism, covalent binding, DNA repair) before manifestation of the effect in question is possible.

Mutagen	Any substance that can cause a change in genetic material. Mutagens have the ability to induce adverse, heritable changes in the genetic material of living organisms.
No observed adverse effects level (NOAEL)	The highest dose at which there is no statistically or biologically significant increase in the frequency of an adverse effect when compared with a control group.
No observed effects level (NOEL)	The highest dose at which there is no statistically or biologically significant increase in the frequency of any effect, adverse or not, compared with a control group.
Order of magnitude	An expression often used in reference to calculations of environmental quantities of risk. Order of magnitude means a factor of 10. For example, 20 (2 x 10) is 1 order of magnitude greater than 2; 200 (2 x 10 x 10) is 2 orders of magnitude greater than 2; and so forth.
Permissible exposure limit (PEL)	PELs are time-weighted average (TWA) air concentrations that must not be exceeded during any 8-hour work shift of a 40-hour workweek as defined by OSHA.
Pharmacokinetics	Study of the absorption, distribution, metabolism, and excretion of chemicals and the genetic, nutritional, behavioral, and environmental factors that modify these parameters.
Pharmacokinetic models	Dose-response models based on the principle that biological effects are the result of biochemical interaction between foreign substances or metabolites and parts of the body.
Physiologically based pharmacokinetic (PBPK) model	A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion.

Probabilistic approaches	Evaluating a range of possible risk estimates and their likelihood, tied to various mathematical models of the likely distribution of potential values, instead of relying on single numbers or point estimates.
Reference concentration (RfC)/reference dose (RfD)	A **reference concentration** is an estimate of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. EPA uses a **reference dose** to express a conservative threshold value for a dose-response relationship for noncarcinogenic effects. It is an estimate of a daily dose to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.
Residual risk	The health risk remaining after risk-reduction actions are implemented, such as risks associated with sources of air pollution that remain after the implementation of maximum achievable control technology.
Risk	The probability that a substance or situation will produce harm under specified conditions. Risk is a combination of two factors: the probability that an adverse event will occur and the consequences of its occurrence (e.g., a specific disease or type of injury).
Risk assessment	The systematic, scientific description of potential adverse effects of exposures to hazardous agents or activities. According to NAS, it involves the four steps of hazard identification, dose-response assessment, exposure assessment, and risk characterization. The product of the risk assessment is a statement regarding the probability that populations, individuals, or environmental entities so exposed will be harmed and to what degree.
Risk characterization	The process of organizing, evaluating, and communicating information about the nature, strength of evidence, and the likelihood of adverse health or ecological effects from particular exposures.

Risk management	The process of analyzing, selecting, implementing, and evaluating actions to reduce risk.
Screening risk assessment	A risk assessment performed using few data and many assumptions to identify exposures that should be evaluated more carefully for their potential risks.
Sensitivity analysis	A method used to examine the behavior of a model by systematically measuring the deviation in its outputs produced as each input, parameter, or assumption is varied from its nominal or base-case value.
Synergistic effects	A term used to describe when the combined biological effects of two risk agents are greater than the sum of the effects of each agent acting alone.
Target organ	The specific organ affected by a dose of a toxic substance, which is not necessarily the organ receiving the highest concentration.
Threshold	The level of exposure above which adverse health effects are thought to occur, and below which no adverse effect is thought to occur.
Threshold dose	Minimum application of a given risk agent required to produce a measurable response.
Threshold effect	An effect for which there is some dose below which the probability of an individual's responding is zero.
Tiered approach	A series of assessments of increasing complexity.
Toxicity	A measure of the degree of harm caused by a specified exposure of human, animal, or plant life to a chemical substance.

Toxicokinetics	The mechanism by which chemical or physical change causes toxic effects.
Toxicology	The study of adverse effects of chemicals on living organisms.
Tumor	Any abnormal growth of tissue in which growth is uncontrolled and progressive.
Uncertainty factor	One of several factors used to calculate an exposure level that will not cause toxicity from experimental data. Uncertainty factors are used to account for the variation in susceptibility among humans, the uncertainty in extrapolating from experimental animal data to humans, the uncertainty in extrapolating from data from studies in which agents are given for less than a lifetime, and other uncertainties such as using LOAEL data instead of NOAEL data.
Variability	A population's natural heterogeneity or diversity, particularly that which contributes to differences in exposure levels or in susceptibility to the effects of chemical exposures.

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