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HUMAN HEALTH RISK ASSESSMENT

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Risk assessment is an ever-evolving process whereby scientific information on the hazardous properties of chemicals and the extent of exposure results in a statement as to the probability that exposed populations will be harmed. The probability of harm can be expressed either qualitatively or quantitatively, depending on the nature of the scientific information available and the intent of the risk assessment. Risk assessment is not research per se, but rather a process of collecting and evaluating existing data. As such, risk assessment draws heavily on the disciplines of toxicology, epidemiology, pathology, molecular biology, biochemistry, mathematical modeling, industrial hygiene, analytical chemistry, and biostatistics. The certainty with which risks can be accurately assessed, therefore, depends on the conduct and publication of basic and applied research relevant to risk issues. While firmly based on scientific considerations, risk assessment is often an uncertain process requiring considerable judgment and assumptions on the part of the risk assessor. Ultimately, the results of risk assessments are integrated with information on the consequences of various regulatory options in order to make decisions about the need for, method of, and extent of risk reduction.

It is clear that society is willing to accept some risks in exchange for the benefits and conveniences afforded by chemical use. After all, we knowingly apply pesticides to increase food yield, drive pollutant-emitting automobiles, and generate radioactive wastes in the maintenance of our national defense. We legally discharge the by-products of manufacturing into the air we breathe, the water we drink, and the land on which our children play. In addition, we have a history of improper waste disposal, the legacy of which is thousands of uncontrolled hazardous waste sites. To ensure that the risks posed by such activities are not unacceptably large, it is necessary to determine safe exposure levels in the workplace and environment. Decisions must also be made on where to locate industrial complexes, on remediation options for hazardous waste sites, tolerance levels for pesticides in foods, safe drinking water standards, air pollution limits, and the use of one chemical in favor of another. Risk assessment provides the tools to make such determinations.

This chapter provides an overview of the risk assessment process and discusses:

- The basic steps of risk assessment
- How risk assessments are performed in a regulatory context
- Differences between human health and ecological risk assessments
- Differences in the estimation of cancer and noncancer risks
- Differences between deterministic and probabilistic risk assessments
- Issues associated with estimating risks from chemical mixtures
- Comparisons of risks from chemical exposure with other health risks
- Risk communication from chemical exposure with other health risks

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23.1 RISK ASSESSMENT BASICS

A Basic Risk Assessment Paradigm

In 1983, the National Research Council described risk assessment as a four-step analytical process consisting of hazard identification, dose–response assessment, exposure assessment, and risk characterization. These fundamental steps have achieved a measure of universal acceptance and provide a logical framework to assemble information on the situation of potential concern and provide risk information to inform decision making (Figure 23.1). The process is rigid enough to provide some methodological consistency that promotes the reliability, utility, and credibility of risk assessment outcomes, while at the same time allowing for flexibility and judgment by the risk assessor to address an endless variety of risk scenarios. Each step in the four-step process known as *risk assessment* is briefly discussed below.

Step 1: Hazard Identification. The process of determining whether exposure to a chemical agent, under any exposure condition, can cause an increase in the incidence or severity of an adverse health effect (cancer, birth defect, neurotoxicity, etc.). Although the matter of whether a chemical can, under any exposure condition, cause cancer or other adverse health effect is theoretically a yes/no question; there are few chemicals for which the human data are definitive. Therefore, laboratory animal studies, *in vitro* tests, and structural and mechanistic comparability to other known chemical hazards are considered in addition to the epidemiological data. This step is common to qualitative and quantitative risk assessment.

Step 2: Dose–Response Assessment. The process of characterizing the relationship between the dose of a chemical and the incidence or severity of an adverse health effect in the exposed population. A dose–response assessment factors not only in the magnitude, duration, and frequency of exposure but also other potential response-modifying variables such as age, sex, and certain lifestyle factors. A dose–response assessment frequently requires extrapolation from high to low doses and from animals to humans.

Step 3: Exposure Assessment. The process of specifying the exposed population, identifying potential exposure routes, and measuring or estimating the magnitude, duration, and frequency of exposure. Exposure can be assessed by direct measurement or estimated with a variety of exposure models. Exposure assessment can be quite complex because exposure frequently occurs

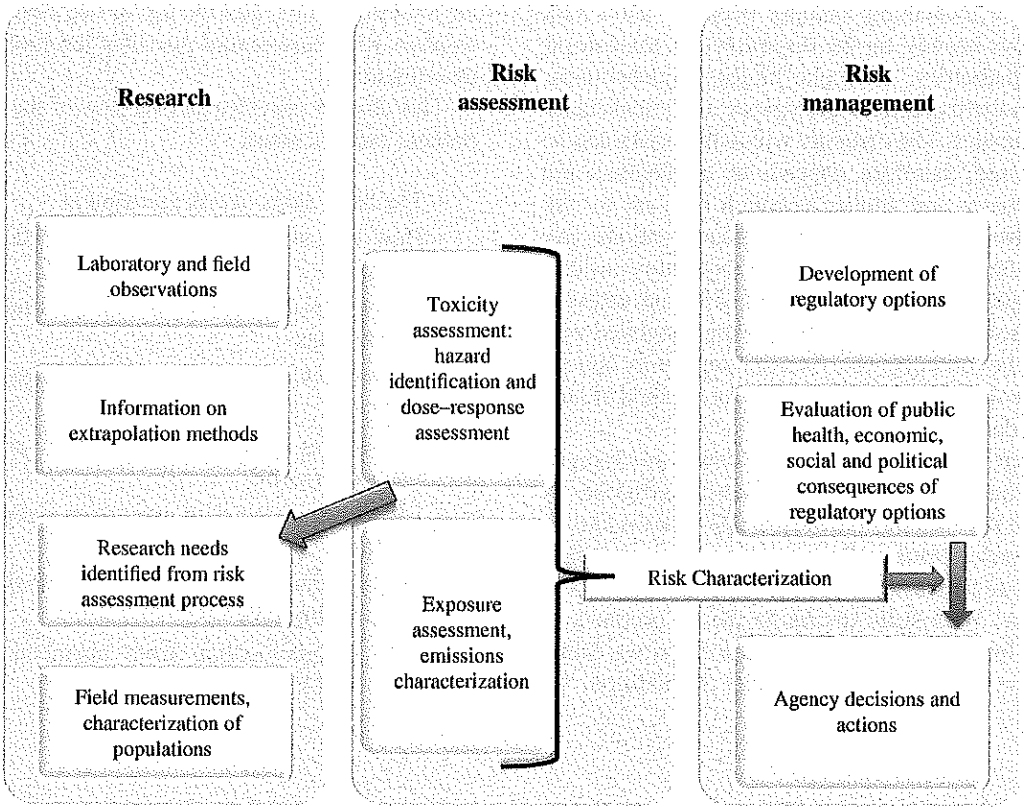

FIGURE 23.1 Elements of risk assessment and risk management. Risk assessment provides a means to organize and interpret research data in order to inform decisions regarding human and environmental health. Through the risk assessment process, important data gaps and research needs are often identified, assisting in the prioritization of basic and applied toxicological research. *Source:* Adapted from NRC (1983).

to a mixture of chemicals from a variety of sources (air, water, soil, food, etc.).

Step 4: Risk Characterization. The integration of information from steps 1 to 3 to develop a qualitative or quantitative estimate of the likelihood that any of the hazards associated with the chemical(s) of concern will be realized. The characterization of risk must often encompass multiple populations having varying exposures and sensitivities. This step is particularly challenging as a variety of data must be assimilated and communicated in such a way as to be useful to everyone with an interest in the outcome of the risk assessment. This may include not only governmental and industry risk managers but also the public as well. This step includes a descriptive characterization of the nature, severity, and route dependency of any potential health effects, as well as variation within the population(s) of concern. Any uncertainties and limitations in the analysis are described in the risk characterization, so that the strengths, weaknesses, and overall confidence in the risk estimates can be understood.

Circumstances may exist in which no risk can be inferred from an exposure assessment that reveals no opportunity for individuals to receive a dose of the chemical. Therefore, situations sometimes exist where a comprehensive risk assessment is unnecessary. In such instances, it may be more practical to communicate findings in a qualitative manner, that is, to state it is highly unlikely chemical X will pose any significant health risk because there is no exposure to the chemical. At other times, quantitative expressions of risk might be more appropriate, as in the case of a population chronically exposed to a known human carcinogen in drinking water. An expression of such risk might be that the lifetime excess cancer risk from exposure is 3 in 1,000,000 (or 3×10^{-6}). Often, such numerical expressions of risk convey an unwarranted sense of precision by failing to communicate the uncertainty inherent in their derivation. They may also prove difficult for nontechnical audiences to comprehend. On the other hand, qualitative risk estimates may appear more subjective and not invoke the same degree of confidence in the risk assessment findings as a numerical expression of risk. Also, qualitative expressions of risk do not readily allow for comparative risk analyses, a useful exercise for putting added risk into context. Although addressed later in this chapter, it is worth mentioning here that effective risk communication plays a key role in utilizing risk assessment findings for the protection of public health.

Risk Assessment in a Regulatory Context: The Issue of Conservatism

Regulatory agencies charged with protecting public health and the environment are constantly faced with the challenge of setting permissible levels of chemicals in the home, workplace, and natural environment. For example, the Occupational Safety and Health Administration (OSHA) is responsible for setting limits on chemical exposure in the workplace, the Food and Drug Administration (FDA) has permissible limits on chemicals such as pesticides in the food supply, and the Environmental Protection Agency (U.S. EPA) regulates chemical levels in air, water, and sometimes soil. Ideally, the level of chemical contamination or residues in many of these media (food, water, air, etc.) would be zero, but this simply is not feasible in a modern industrial society. Although it may not be possible to completely eliminate the presence of unwanted chemicals from the environment, there is almost universal agreement that we should limit exposures to these chemicals to levels that do not cause illness or environmental destruction. The process by which regulatory agencies set limits with this goal in mind is a combination of risk assessment and risk management.

The risks associated with chemical exposure are not easily measured. While studies of worker health have been extremely valuable in assessing risks and setting standards for occupational chemical exposure, determining risks from lower doses typically associated with environmental exposures has been difficult. Epidemiologic studies of environmental chemical exposure can provide some estimate of increased risk of specific diseases associated with a particular chemical exposure compared with a control population, but there are several problems in attempting to generalize the results of such studies. Exposure of a population is often difficult to quantify, and the extrapolation of observations from one situation to another (e.g., different populations, different manners of exposure, different exposure levels, different exposure durations) is challenging. For the most part, risk assessments for environmental chemical exposures must rely on modeling and assumptions to generate estimates of potential risks. Because these risk estimates usually cannot be verified, they represent hypothetical or theoretical risks. This is an important facet of risk assessment that is often misunderstood by those who erroneously assume that risk estimates for environmental chemical exposure have a strong empirical basis.

As discussed in subsequent sections, there are many sources of uncertainty in deriving risk estimates. Good data regarding chemical exposure and uptake are seldom available, forcing reliance on models and assumptions that may or may not be valid. Toxicity information often must be extrapolated from one species to another (e.g., use of data from laboratory mice or rats for human health risk assessment), from one route of exposure to another (e.g., use of toxicity data following ingestion to evaluate risks from dermal exposure), and from high doses to the lower doses more commonly encountered with environmental exposure. In view of all of these uncertainties, it is impossible to develop precise estimates of risks from chemical exposures. Choices made by the risk assessor, such as

which exposure model to use or how to scale doses when extrapolating from rodents to humans, can have a profound impact on the risk estimate.

Regulatory agencies address uncertainty in risk assessments by using conservative approaches and assumptions; that is, in the face of scientific uncertainty, they will select models and assumptions that tend to overestimate, rather than underestimate, risk so as to be health protective. Since most risk assessments are by, or for, regulatory agencies, this conservatism is a dominant theme in risk assessments and a continuous source of controversy. Some view the conservatism employed by regulatory agencies as excessive, resulting in gross overestimation of risks and unwarranted regulations that waste billions of dollars. Others question whether regulatory agencies are conservative enough and suggest that the public (particularly more sensitive individuals such as children) may not be adequately protected by contemporary risk assessment approaches.

Defining Risk Assessment Problems

A coherent risk assessment requires a clear statement of the risk problem to be addressed. This should be developed very early in the risk assessment process and is shaped by the question(s) the risk assessment is expected to answer. Ideally, both the risk assessor(s) and the individuals or organizations that will ultimately use the risk assessment will have input. This helps ensure that the analysis will be technically sound and serve its intended purpose.

One of the first issues to address is which chemicals or agents should be included in the analysis. In some situations, this may be straightforward, such as a risk assessment focused specifically on occupational exposure to a particular chemical. In other circumstances, the chemicals of concern may not be obvious. An example of this would be risk assessment for a chemical disposal site where the chemicals present and their amounts are initially unknown. A related issue is which health effects the risk assessment should address. While it is tempting to answer "all of them," it must be recognized that each chemical in a risk assessment is capable of producing a variety of adverse health effects, and the dose–response relationships for these effects can vary substantially. Developing estimates of risks for each of the possible adverse effects of each chemical of interest is usually impractical. A simpler approach is to estimate risks for the health effect to which individuals are most sensitive, specifically, the one that occurs at the lowest dose. If individuals can be protected from this effect, whatever it might be, they will logically be protected from all other effects. Of course, this approach presumes that the most sensitive effect has been identified and dose–response relationship information for this effect exists. Obviously, for this approach to be effective, the toxicology of each chemical of interest must be reasonably well characterized.

In defining the risk problem, populations potentially at risk must be identified. These populations would be groups of individuals with distinct differences in exposure, sensitivity to toxicity, or both. For example, a risk assessment for a contaminated site might include consideration of workers at the site, occasional trespassers or visitors to the site, or individuals who live at the site if the land is (or might become) used for residential purposes. If residential land use is contemplated, risks are often calculated separately for children and adults, since they may be exposed to different extents and therefore have different risks. Depending on the goals of the risk assessment, risks may be calculated for one or several populations of interest.

Many chemicals move readily in the environment from one medium to another. Thus, a chemical spilled on the ground can volatilize into the air, migrate to groundwater and contaminate a drinking water supply, or be carried with surface water runoff to a nearby stream or lake. Risk assessments have to be cognizant of environmental movement of chemicals and the fact that an individual can be exposed to chemicals by a variety of pathways. In formulating the risk problem, the risk assessor must determine which of many possible pathways are complete; that is, which pathways will result in movement of chemicals to a point where contact with an individual will occur. Each complete pathway provides the opportunity for the individual to receive a dose of the chemical and should be considered in some fashion in the risk assessment. Incomplete exposure pathways—those that do not result in an individual coming in contact with contaminated environmental media (e.g., air, water, soil)—can be ignored because they offer no possibility of receiving a dose of chemical and therefore pose no risk.

Risk assessments can vary considerably in the extent to which information on environmental fate of contaminants is included in the analysis. Some risk assessments, for example, have attempted to address risks posed by chemicals released to the air in incinerator emissions. These chemicals are subsequently deposited on the ground where they are taken up by forage crops that are consumed by dairy cattle. Consumption of meat or milk from these cattle is regarded as a complete exposure pathway from the incinerator to a human receptor. As the thoroughness of the risk assessment increases, so does the complexity. As a practical matter, complete exposure pathways that are thought to be minor contributors to total exposure and risk are often acknowledged but not included in the calculation of risk to make the analysis more manageable.

Often, exposure can lead to uptake of a chemical by more than one route. For example, contaminants in soil can enter the body through dermal absorption, accidental ingestion of small amounts of soil, or inhalation of contaminants volatilized from soil or adherent to small dust particles. Consequently, the manner of anticipated exposure is important to consider, as it will dictate the routes of exposure (i.e., inhalation, dermal contact, or ingestion) that need to be included in the risk assessment for each exposure scenario.

Human Health versus Ecological Risk Assessments: Fundamental Differences

Ecological risk assessments are defined as those that address species other than humans, namely, plant and wildlife populations. Problem formulation is more challenging when conducting ecological risk assessments. Instead of one species, there are several to consider. Also, the exposure pathway analysis is more complicated, at least in part because some of the species of interest consume other species of interest, thereby acquiring their body burden of chemical. Unlike human health risk assessments, where protection of individuals against any serious health impact is nearly always the objective, goals for ecological risk assessments are often at the population, or even ecosystem, level rather than focusing on individual plants and animals. Consequently, development of assessment and measurement endpoints consistent with the goals of the ecological risk assessment is essential in problem formulation for these kinds of analyses.

Historically, the risk assessment process has focused primarily on addressing potential adverse effects to exposed human populations, and the development of well-defined methods for human health risk assessment preceded those for ecological risk assessment. However, increasing concern for ecological impacts of chemical contamination has led to a "catching up" in risk assessment methodology. While detailed methods for both human health and ecological risk assessment are now in place, they are not identical. The conceptual basis may be similar, including some form of hazard identification, exposure assessment, dose–response assessment, and risk characterization. However, there are some important differences in approaches, reflecting the reality that there are some important differences in evaluating potential chemical effects in humans versus plants and wildlife.

The most obvious difference between human health and ecological risk assessments is that the ecological risk assessments are inherently more complicated. Human health risk assessments, of course, deal with only one species. Ecological risk assessments can involve numerous species, many of which may be interdependent. Given the nearly endless array of species of plants and animals that might conceivably be affected by chemical exposure, there must be some process to focus on species that are of greatest interest to keep the analysis to a manageable size. A species may warrant inclusion in the analysis because it is threatened or endangered, because it is a species on which many others depend (e.g., as a food source), or because it is especially sensitive to toxic effects of the chemical and can therefore serve as a sentinel for effects on other species.

The increased complexity of analysis for ecological risk assessments extends to evaluation of exposure. In human health risk assessment, the potential pathways by which the chemical(s) of interest can reach individuals must be assessed and, if possible, the doses of chemicals received by these pathways estimated. In an ecological risk assessment, the same process must be undertaken, but for several species instead of just one. Also, an ecological risk assessment typically must evaluate food chain exposure. This is particularly important when chemicals of interest tend to bioaccumulate, resulting in very high body burdens in predator species at the top of the food chain. Not only must the potential for bioaccumulation be assessed, but also the escalating doses for species of interest must be estimated according to their position in the food chain. This type of analysis is only included in human health risk assessments when estimating dose from a potential food source (e.g., fish, meat, or milk).

A third distinction between human health and ecological risk assessment lies in the assessment objectives. Human health risk assessments characteristically focus on the most sensitive potential adverse health effect, specifically, that which occurs at the lowest dose. In this way, they are directed to evaluating the potential for *any* health effect to occur. For ecological risk assessments, the analyses generally address only endpoints that affect fecundity (growth, survival, and reproduction). Thus, the goal of an ecological risk assessment might be to determine whether the presence of a chemical in the environment at a particular concentration would result in declining populations for a specific species (e.g., due to mortality or reproductive failure), disappearance of a species in a particular area, or loss of an entire ecosystem, depending on risk management objectives. It is entirely possible that chemical exposure could result in the deaths of many animals, but as long as the populations were stable, the risk would be considered acceptable. The exception to population protection is for species with special legal protection (endangered, threatened, or listed). These species should be protected on an individual level, and all adverse effects should be considered in determining a critical effect.

What constitutes an unacceptable impact is not clearly defined in ecological risk assessment. Regulatory agencies may decide to focus on higher tropic level species or may not focus on a species at all, protecting the habitat instead. Alternatively, biodiversity may be utilized as an ecological endpoint. These alternative endpoints allow for the loss of entire populations and for the establishment of nonnative and invasive species. This reflects philosophical and risk management differences in terms of what constitutes an unacceptable chemical impact on humans versus plants or wildlife.

Because of the greater potential complexity of an ecological risk assessment, more attention must be given to ensuring that an analysis of appropriate scope and manageable size is achieved. For this reason, ecological risk assessments are more iterative in nature than their human health counterparts. An ecological risk assessment begins with a screening-level assessment, which is a form of preliminary investigation to determine whether unacceptable risks to ecological receptors may exist. It includes a review of data regarding chemicals present and their concentrations, species present, and potential

pathways of exposure. It is a rather simplified analysis that uses conservative or worst-case assumptions regarding exposure and toxicity. If the screening analysis finds no indication of significant risks using very conservative models and assumptions, the analysis is concluded. If the results of the screening analysis suggest possible ecological impacts, a more thorough analysis is conducted that might include additional samples of environmental media, taking samples of wildlife to test for body burdens of chemicals, carefully assessing the health status of populations exposed to the chemical, conducting toxicity tests, conducting more sophisticated fate and transport analysis of the chemicals of potential concern, and a more detailed and accurate exposure assessment.

23.2 HAZARD IDENTIFICATION

Hazard identification involves an assessment of the intrinsic toxicity of the chemical(s) of potential concern. This assessment attempts to identify health effects characteristically produced by the chemical(s) that may be relevant to the risk assessment. While this may appear to be a straightforward exercise, in reality, it requires a good deal of careful analysis and scientific judgment. The reason for this is that the risk assessor rarely has the luxury of information that adequately describes the toxicity of a chemical under the precise set of circumstances to be addressed in the risk assessment. Instead, the risk assessor typically must rely on incomplete data derived from species other than the one of interest under exposure circumstances very different from those being evaluated in the risk assessment. The existence in the scientific literature of poorly designed studies with misleading results and conclusions, as well as conflicting data from seemingly sound studies, further complicates the task.

This section of the chapter discusses some of the considerations when reviewing and evaluating the toxicological literature for assessment of intrinsic toxicity. Many of these considerations address suitability of data for extrapolation from one set of circumstances to another, while others pertain to the fundamental reliability of the information. Much of the discussion regarding extrapolation deals with assessing the value of animal data in predicting responses in humans, since human health risk assessments are forced to rely predominantly on animal studies for toxicity data. Keep in mind that most of the same extrapolation issues are equally relevant for ecological risk assessments, where often toxicity in wildlife species has to be inferred from data available only from laboratory animal species.

Information from Epidemiologic Studies and Case Reports

Observations of toxicity in humans can be extremely valuable in hazard identification. They offer the opportunity to test the applicability of observations made in animal studies to humans and may even provide an indication of the relative potency of the chemical in humans versus laboratory animal models. If the human studies are of sufficient size and quality, they may stand alone as the basis for hazard identification in human health risk assessment.

Despite the attractiveness of human studies, they often have significant limitations. A less-than-rigorous effort to properly match exposed and control populations makes it difficult or impossible to attribute observed differences in health effects to chemical exposure with any confidence. Even in well-designed epidemiologic studies, there is always the possibility that an unknown critical factor causally related to the health effect of interest has been missed. For this reason, a consistent association between chemical exposure and a particular effect in several studies is important in establishing whether the chemical produces that effect in humans.

Other criteria in evaluating epidemiologic studies include the following:

- The positive association (correlation) between exposure and effect must be seen in individuals with definitive exposure.
- The positive association cannot be explained by bias in recording, detection, or experimental design.
- The positive association must be statistically significant.
- The positive association should show both dose and exposure duration dependence.

Information from Animal Studies

Typically, data from studies using laboratory animals must be used for some or all of the intrinsic toxicity evaluation of a chemical in humans. There are several aspects that need to be considered when interpreting the animal data, as discussed below.

Breadth and Variety of Toxic Effects The toxicological literature should be reviewed in terms of the types of effects observed in various test species. This is an important first step in chemical toxicity evaluation because:

- It identifies potential effects that might be produced in humans. To some extent, the consistency with which an effect is observed among different species provides greater confidence that this effect will occur in humans as well. An effect that occurs in some species but not others, or one sex but not the other, signals that great care will be needed in extrapolating findings in animals to humans without some form of corroborating human data.
- A comparison of effects within species (e.g., sedation vs. hepatotoxicity vs. lethality) helps establish a rank order of the toxic effects manifested as the dose increases. This

aids in identifying the most sensitive effect. Often, this effect becomes the focus of a risk assessment, since protecting against the most sensitive effect will protect against all effects. Also, comparisons of dose–response relationships within species can provide an estimation of the likelihood that one toxic effect will be seen given the appearance of another.

Mechanism of Toxicity Understanding the mechanism of action of a particular chemical helps establish the right animal species to use in assessing risk and to determine whether the toxicity is likely to be caused in humans. For example, certain halogenated compounds are mutagenic and/or carcinogenic in some test species but not others. Differences in carcinogenicity appear to be related to differences in metabolism of these chemicals because metabolism is an integral part of their mechanism of carcinogenesis. For these chemicals, then, a key issue in selecting animal data for extrapolation to humans is the extent to which metabolism in the animal model resembles that in humans. A second example is renal carcinogenicity from certain chemicals and mixtures, including gasoline. Gasoline produces renal tumors in male rats, but not female rats or mice of either sex. The peculiar susceptibility of male rats to renal carcinogenicity of gasoline can be explained by its mechanism of carcinogenesis. Metabolites of gasoline constituents combine with a specific protein, α-2μ-globulin, to produce recurring injury in the proximal tubules of the kidney. This recurring injury leads to renal tumors. Female rats and mice do not accumulate this protein in the kidney, explaining why they do not develop renal tumors from gasoline exposure. Humans also do not accumulate the protein in the kidney, making the male rat a poor predictor of human carcinogenic response in this situation.

In a sense, choosing the best animal model for extrapolation is always a catch-22 situation. Selection of the best model requires knowledge of how the chemical behaves in both animals and humans, including its mechanism of toxicity. In the situations in which an animal model is most needed (when we have little data in humans), we are in the worst position to select a valid model. The choice of an appropriate animal model becomes much clearer when we have a very good understanding of the toxicity in humans and animals, but in this situation, there is, of course, much less need for an animal model.

In addition to helping identify the best species for extrapolation, knowledge of the mechanism of toxicity can assist in defining the conditions required to produce toxicity. This is an important aspect of understanding the hazard posed by a chemical. For example, acetaminophen, an analgesic drug used in many over-the-counter pain relief medications, can produce fatal liver injury in both animals and humans. By determining that the mechanism of toxicity involves the production of a toxic metabolite during the metabolism of high doses, it is possible to predict and establish its safe use in humans, determine the consequences of various doses, and develop and provide antidotal therapy.

Dosages Tested Typically, animal studies utilize relatively high doses of chemicals so that unequivocal observations of effect can be obtained. These doses are usually much greater than those received by humans, except under unusual circumstances such as accidental or intentional poisonings. Thus, while animal studies might suggest the possibility of a particular effect in humans, that effect may be unlikely or impossible at lower dosages associated with actual human exposures. The qualitative information provided by animal studies must be viewed in the context of dose–response relationships. Simply indicating that an effect might occur is not enough; the animal data should indicate at what dosage the effect occurs and, equally importantly, at what dosage the effect does *not* occur.

Validity of Information in the Literature Any assessment of the intrinsic toxicity of a chemical begins with a comprehensive search of the scientific literature for relevant studies. While all of the studies in the literature share the goal of providing new information, the reality of the situation is that all are not equally valuable. Studies may be limited by virtue of their size, experimental design, methods employed, or the interpretations of results by the authors. These limitations are sometimes not readily apparent, requiring that each study be evaluated carefully and critically. The following are some guidelines to consider when evaluating studies:

- Has the test used an unusual, new, or unproven procedure?
- Does the test measure toxicity directly, or is it a measure of a response purported to indicate an eventual change (a pretoxic manifestation)?
- Have the experiments been performed in a scientifically valid manner?
- Are the observed effects statistically significant against an appropriate control group?
- Has the test been reproduced by other researchers?
- Is the test considered more or less reliable than other types of tests that have yielded different results?
- Is the species a relevant or reliable human surrogate, or does this test conflict with other test data in species phylogenetically closer to humans?
- Are the conclusions drawn from the experiment justified by the data, and are they consistent with the current scientific understanding of the test or area of toxicology?
- Is the outcome of the reported experiment dependent on the test conditions, or is it influenced by competing toxicities?
- Does the study indicate causality or merely suggest a correlation that could be due to chance?

Other Considerations Numerous confounders can affect the validity of information derived from animal studies and its application or relevance to human exposure to the same chemical. Issues regarding selection of the appropriate species for extrapolation are discussed in Section 23.2. Even if the selection of species is sound, certain other characteristics of the experimental animals can influence toxic responses and therefore the extrapolation of these responses to humans. Examples include the age of the animal (e.g., whether studies in adult animals are an appropriate basis for extrapolation to human children), the sex of the animal (obviously, studies limited to just male or female animals cannot address all of the potential toxicities for both sexes of humans), disease status (e.g., whether results obtained in healthy animals are relevant to humans with preexisting disease, and vice versa), nutritional status (e.g., whether studies in fasted animals accurately reflect what occurs in fed humans), and environmental conditions.

Other confounders go beyond the animal models themselves and pertain to the type of study conducted. For example, studies involving acute exposure to a chemical are usually of limited value in understanding the consequences of chronic exposure, and chronic studies generally offer little insight into consequences of acute exposure. This is because chronic toxicities are often produced by mechanisms different from those associated with acute toxicities. For this reason, good characterization of the intrinsic toxicity of a chemical requires information from treatments of varying duration, ranging from a single dose to exposure for a substantial portion of the animal's lifetime.

Information from *In Vitro* and In Silico Studies

In vitro and in silico studies are useful for predicting whether toxicity might occur as a result of exposure. The high cost of animal toxicity testing and large number of chemicals yet to be tested make these methods valuable tools for predicting hazard. *In vitro* studies include cells in culture, isolated tissues, tissue extracts or homogenates, subcellular fractions, and purified biochemical reagents (e.g., enzymes, other proteins, nucleic acids). The basis of their use in hazard identification is for determining the mechanism or mode of action and understanding how the chemical causes effects at the cellular, biochemical, and molecular level. Due to the complexity of an intact biological system, *in vitro* results cannot be extrapolated to a toxic endpoint. However, toxic effects can be predicted from these studies and verified in animal models. In silico studies include structure–activity relationships (SAR). They utilize computer modeling to predict biological activity and potency from the chemical structure. The most frequent use of in silico modeling is to predict a common mode of action for an entire class of chemicals. The Ah receptor binding ability of dioxin-like compounds was predicted in silico based on SAR.

23.3 DOSE–RESPONSE ASSESSMENT

In this portion of the risk assessment, the dose–response relationships for the toxicities of concern must be measured, modeled, or assumed, in order to predict responses to doses estimated in the exposure assessment. While dose–response relationships could theoretically be obtained for a variety of effects from each chemical of potential concern, in practice, attention is usually centered on the most sensitive effect of the chemical.

In risk assessment, two fundamentally different types of dose–response relationships are thought to exist. One is the threshold model, in which all doses below some threshold produce no effect, while doses above the threshold produce effects that increase in incidence or severity as a function of dose. The second model has no threshold—any finite, nonzero dose is thought to possess some potential for producing an adverse effect. The derivation of these two types of dose–response relationships and their use to provide estimates of risk are very different, as described in the following sections.

Threshold Models

For all toxicities other than cancer, there is some dose below which no observable or statistically measurable response exists. This dose, called the *threshold dose*, was graphically depicted in Chapter 1 (see also Figure 23.2). Conceptually, a threshold makes sense for most toxic effects. The body possesses a variety of detoxification and cell defense and repair mechanisms, and below some dose (i.e., the threshold dose), the magnitude of effect of the chemical is so small that these detoxification and defense/repair mechanisms render it undetectable.

In the most common form of threshold dose–response modeling, the threshold dose becomes the basis for establishing a "safe human dose" (SHD). Because we rarely, if ever, are able to define the true threshold point on the dose–response curve, the threshold dose is usually approximated. There are two methods for estimating the threshold. These methods include the no observable adverse effect level (NOAEL)/lowest observable adverse effect level (LOAEL) approach and the benchmark dose (BMD) approach. The preferred method is the BMD approach, which derives a threshold dose based on the dose–response curve. If data are not amenable to the BMD approach, then the NOAEL/LOAEL approach is utilized.

In the NOAEL/LOAEL approach, the more desirable method uses the highest reported dose or exposure level for which no toxicity was observed. This dose, known as the "NOAEL," is considered for practical purposes to represent the threshold dose. This prevents underestimating the toxicity of a chemical. Sometimes, the available data do not include a NOAEL; that is, all of the doses tested produced some measurable toxic effect. In this situation, the lowest dose producing an adverse effect, termed the

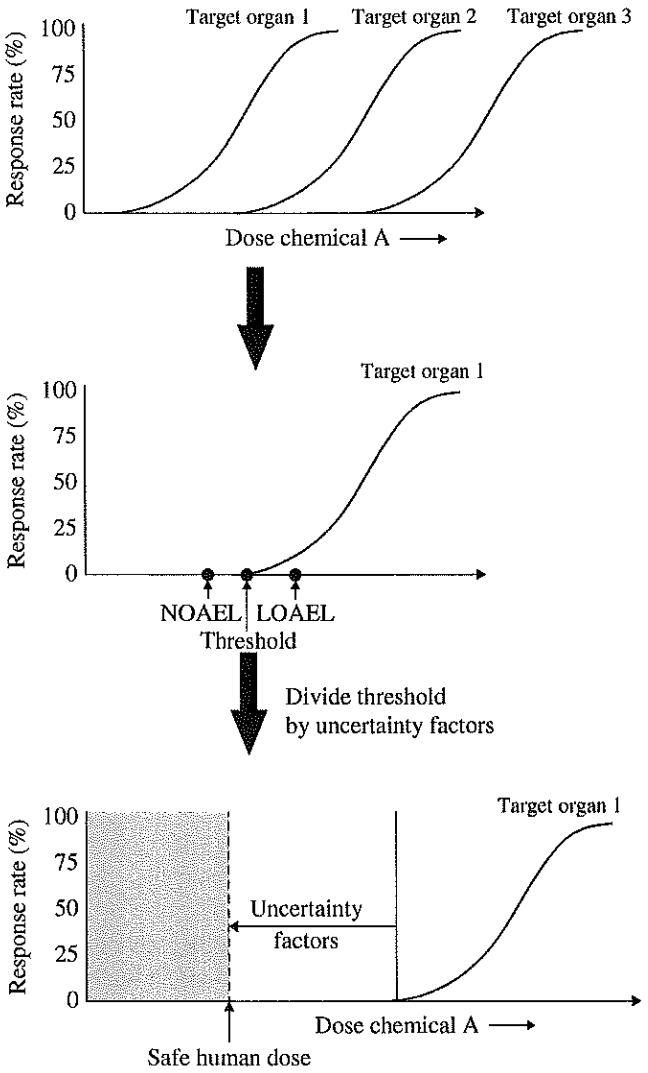

FIGURE 23.2 Estimation of a safe human dose (SHD). The first step is identification of the target organ or effect most responsive to the chemical (in this case, target organ 1 in the upper panel). Dose–response data for this effect are used to identify no observable adverse effect level (NOAEL) and/or lowest observable adverse effect level (LOAEL) doses in order to approximate the threshold dose. Either the NOAEL or LOAEL is divided by a series of uncertainty factors to generate the SHD.

"LOAEL," is identified from the dose–response data. The threshold dose will lie below, and hopefully near, this dose. A threshold dose is then projected from the LOAEL, usually by dividing the LOAEL by a factor of 10 (see Figure 23.2). There are several limitations to the NOAEL/LOAEL methodology. One limitation is that the ability of the NOAEL to approximate the threshold dose is dependent on dose selection and spacing in available studies, and in many cases, these are not well suited to determining the threshold. If the doses are spaced far apart, the NOAEL may be much lower than the actual threshold dose and result in an overestimation of toxicity. A second limitation is that the approach fails to consider the shape or slope of the dose–response curve, focusing instead on results from one or two low doses exclusively. This is especially important at lower, environmentally relevant concentrations where small changes in dose can result in large changes in effect. Another limitation is that studies with small numbers of animals may result in higher thresholds since there is not enough power in those studies to identify effects that occur with low frequencies. Therefore, poor study design can be rewarded with a higher threshold dose.

The second method for estimating a threshold dose is the BMD approach. This method utilizes all of the dose–response data and is not dependent on any single data point. In this approach, dose–response data for the toxic effect of concern are fit to a mathematical model, and the model is used to determine the dose corresponding to a predetermined benchmark response. For most quantal data, the dose at which 10% of the population exhibits a response (effective dose$_{10}$ (ED_{10})) is chosen as the benchmark response. Exceptions include reproductive data (5% level) and human data (1% level) for which lower benchmarks are utilized. For continuous data, the benchmark response is a 10% change in endpoint that is considered to be biologically significant or a change of the treated mean equal to one standard deviation from the control mean. As an example, dose–response data might be used to determine the dose required to produce a 10% incidence of liver toxicity from mice treated with a chemical. This dose would be referred to as the ED_{10} or dose effective in producing a 10% incidence of effect. Often, for regulatory purposes, statistical treatment of the data is used to derive upper and lower confidence limit estimates of this dose. The more conservative of these is the lower confidence limit estimate of the dose, which in this case would be designated as the $BMDL_{10}$ (see Figure 23.3). In order to develop an SHD from the ED_{10} or the $BMDL_{10}$, a series of uncertainty factors would be applied, analogous to the NOAEL approach. In a sense, the BMD approach is like extrapolating an SHD from a NOAEL, except the BMD is much more rigorously defined.

The BMD approach works best if there are response data available for a variety of doses. In order to derive an accurate estimate of the threshold dose utilizing the BMD approach, a statistically or biologically significant dose-related trend is necessary. Without a trend, the software will not be able to accurately model the data. Additionally, if there is no NOAEL, the LOAEL must be near the true threshold. Otherwise, there is too much uncertainty in the models (the BMDL will be model dependent), and the software will not be able to reproduce the shape of the curve in the threshold region with any certainty. In this case, the BMD approach would not provide any additional information as to the location of the threshold dose. In these instances, the NOAEL/LOAEL approach should be used.

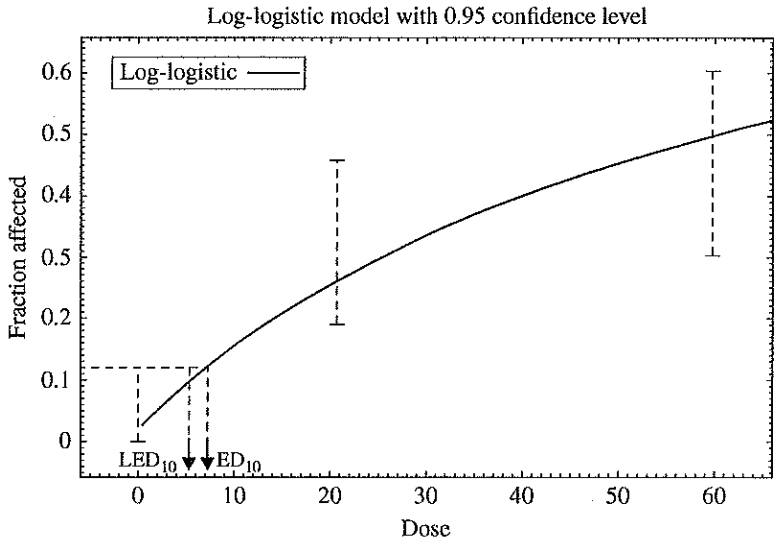

FIGURE 23.3 Derivation of the benchmark dose (BMD). Dose–response data for the toxic effect of concern are fit to a mathematical model, depicted by the solid line. This model is used to determine the effective dose (ED) corresponding to a predetermined benchmark response (BMR) (e.g., 10% of the animals responding), which is termed the BMD. Statistical treatment of the data can be used to derive the lower confidence limit estimate of the BMD, termed the BMDL. Either the BMD or BMDL may be used to represent the point of departure, although the more conservative BMDL is typically used for regulatory purposes. *Source:* Adapted from USEPA (2012).

From the estimates of the threshold dose, an SHD can be calculated. Different agencies have different terminologies that they apply to the SHD; the U.S. EPA refers to this dosage as a "reference dose" (RfD), or, if it is in the form of a concentration of chemical in air, as a "reference concentration" (RfCs). Other agencies have adopted different terminologies; for example, the U.S. FDA uses the term "allowable daily intake" (ADI). The basic concept is the same, and the approach to the development of an SHD is relatively simple, as illustrated in the flow diagram in Figure 23.2. Because a chemical may produce more than one toxic effect, the first step is to identify from the available data the adverse effect that occurs at the lowest dose. Second, the threshold dose or some surrogate measure of the threshold dose (e.g., the NOAEL or LOAEL reduced by some amount) is identified for the most sensitive toxic endpoint. The threshold dose (or its surrogate measure) is then divided by an uncertainty factor to derive the SHD, and this dose can then be converted into an acceptably safe exposure guideline for that chemical.

Calculating Safety for Threshold Toxicities: The SHD Approach

The calculation of an SHD essentially makes an extrapolation on the basis of the size differential between humans and the test species. This extrapolation is based on a dosimetric adjustment factor that accounts for toxicokinetic and some toxicodynamic differences between species. The calculation is similar to the following:

$$\text{SHD} = \frac{\text{NOAEL(mg/kg per day)} \times (\text{BW}_a / \text{BW}_h)^{1/4}}{\text{UF}}$$
$$= N\,\text{mg/kg·day}$$

where

NOAEL = threshold dose or some other no observable adverse effect level selected from the no-effect region of the dose–response curve;

SHD = safe human dose;

UF = the total uncertainty factor, which depends on the nature and reliability of the animal data used for the extrapolation;

N = number of milligrams consumed per kilogram per day;

BW_a = body weight of the animal; and

BW_h = human body weight.

Typically, the uncertainty factor used varies from 10 to 10,000 and is dependent on the confidence placed in the animal database as well as whether there are human data to substantiate the reliability of the animal no-effect levels that have been reported. Of course, the number calculated should use chronic exposure data if chronic exposures are expected. This type of model calculates one value, the expected safe human dosage, that regulatory agencies have referred to as either the ADI or the RfD. Exposures, which produce human doses that are at or below these safe human dosages (ADIs or RfDs), are considered safe.

Example Calculation Pentachlorophenol (PCP), a general-purpose biocide, will be used as an example of how to derive

a safe human dosage. A literature review of the noncarcinogenic effects of PCP has shown that the toxicological effect of greatest concern is its hepatotoxic effects in test animals. The PCP LOAEL for these effects has been reported to be 1.5 mg/kg daily. Using the formulas shown in the previous text and an uncertainty factor of 300, an SHD could be calculated as follows:

$$\text{SHD} = \frac{1.5\text{mg/kg daily} \times (12\text{kg}/70\text{kg})^{1/4}}{300}$$

$$\text{SHD} = 0.0032\text{mg/kg} \cdot \text{day}$$

Once the SHD has been estimated, it may be necessary to convert the dose into a concentration of the chemical in a specific environmental medium (air, water, food, soil, etc.) that corresponds to a safe exposure level for that particular route of exposure. That is, while some dose (in mg/kg · day) may be the total safe daily intake for a chemical, the allowable exposure level of that chemical will differ depending on the route of exposure and the environmental medium in which it is found.

Uncertainty Factor The uncertainty factor is really a composite of several uncertainty factors intended to address weaknesses in the data or uncertainties in extrapolation from animals to humans. These uncertainties arise because of our inability to directly measure the actual human threshold dose. The weaker the data set available for evaluation (few studies, limited doses tested, etc.) and the more assumptions required, the greater the uncertainty that the NOAEL or LOAEL from the literature actually represents the threshold dose in humans. The purpose of dividing the NOAEL, LOAEL, or BMD by uncertainty factors is to ensure that the SHD used in the risk assessment is below the actual human threshold dose for toxicity for all individuals in the exposed population, thereby avoiding any underestimation of risk. The greater the uncertainty associated with the data, the larger the uncertainty factor required to insure protection.

The general rationale for selecting the size of the uncertainty factor for a particular area of uncertainty is as follows:

- UF_A—An uncertainty factor of up to 10 is applied in extrapolating toxicity data from one species to another. It is used to account for the possibility that humans are more sensitive to toxicity than the test species. A factor of 10 is utilized as the default value, and a factor of 3 is utilized if the study species is a nonhuman primate or if toxicodynamic and toxicokinetic data allow the calculation of a human equivalent dose (e.g., physiologically based pharmacokinetic (PBPK) modeling, species scaling).
- UF_H—An uncertainty factor of up to 10 is used to account for variability in sensitivity to toxicity among subjects. An uncertainty factor of 10 is applied to ensure that the final toxicity value is protective for sensitive individuals within a population. An uncertainty factor of 3 is utilized if the data is from a sensitive subpopulation known to be more susceptible to the adverse effect. An uncertainty factor of 1 is utilized if human data are available from a particularly vulnerable subpopulation.
- UF_S—An uncertainty factor of up to 10 might be applied if only subchronic data are available. It is possible under these circumstances that the threshold dose for longer exposures might be lower, and this uncertainty factor is intended to protect against this possibility. A factor of 3 is often utilized for an exposure duration that is greater than subchronic, but less than chronic (e.g., 1 year in rodents). An uncertainty factor of 1 is utilized when chronic data are available.
- UF_L—As discussed earlier, an uncertainty factor of up to 10 may be applied if the only value with which to estimate the threshold dose is a LOAEL value. Division by this uncertainty factor is meant to accomplish a reduction in the LOAEL to a level at or below the threshold dose. An uncertainty of 1 is applied when the BMD is utilized as the threshold dose.
- UF_D—An additional uncertainty factor of up to 10 is applied if the overall quality of the database is poor, the number of animal species tested is few, the number of toxic endpoints evaluated is small, or the available studies are found to be deficient in quality. An uncertainty factor of 3 is utilized if either a prenatal toxicity or two-generation reproduction study is absent from the database. If both are absent, an uncertainty factor of 10 should be applied.
- MF—The development of some SHDs incorporates a modifying factor to account for deficiencies in the data set not covered by the other uncertainty factors. In 2002, the U.S. EPA discontinued the use of modifying factors, stating they are sufficiently incorporated in the general database uncertainty factors.

These uncertainty factors are multiplicative; that is, an uncertainty factor of 10 for sensitive individuals combined with an uncertainty factor of 10 for extrapolation of data from animals to humans results in a total uncertainty factor of 100 (10×10). Total uncertainty factors applied to develop an SHD commonly range between 300 and 1000, and values up to 10,000 or more are possible, although regulatory agencies may place a cap on the size of compounded uncertainty factors (e.g., a limit of 3000).

In the example calculation for PCP earlier, an uncertainty factor of 300 was utilized to calculate the SHD. Uncertainty factors were used to account for animal to human extrapolation, variability among humans in sensitivity, and the use of a LOAEL (UF_A of $10 \times UF_H$ of $10 \times UF_S$ of $1 \times UF_L$ of $3 \times UF_D$ of $1 = 300$).

Quantifying Noncancer Risk

Although the term "risk" often implies probability of an adverse event, the threshold approach to assessing chemical risk does not result in risk expression in probability terms. This approach is instead directed to deriving a safe limit for exposure and then determining whether the measured or anticipated exposure exceeds this limit. All doses or exposures below this "safe level" should carry the same chance that toxicity will occur—namely, zero. With this model, the acceptability of the exposure is basically judged in a "yes/no" manner. The most common quantitative means of expressing hazard for noncancer health effects is through a hazard quotient (HQ). Agencies such as the U.S. EPA calculate an HQ as the estimated dose from exposure divided by their form of the SHD, the RfD:

$$\mathrm{HQ} = \frac{D}{\mathrm{RfD}} \left(\text{or } \mathrm{HQ} = \frac{D}{\mathrm{SHD}} \right)$$

where

HQ = hazard quotient,

D = dosage (mg/kg · day) estimated to result from exposure via the relevant route, and

RfD = reference dose (mg/kg · day).

Interpretation of the HQ is relatively straightforward if the value is less than one. This means that the estimated exposure is less than the SHD and no adverse effects would be expected under these circumstances. Interpretation of HQ values greater than one is more complicated. A value greater than one indicates that the estimated exposure exceeds the SHD, but recall that the SHD includes a number of uncertainty factors that impart a substantial margin of safety. Therefore, exposures that exceed the SHD, but lie well within this margin of safety, may warrant further analysis but are unlikely to produce adverse health effects.

Dose–response relationships can vary from one route of exposure to another (e.g., a safe dose for inhalation of a chemical may be different from a safe dose for its ingestion). As a result, a given chemical may have different SHDs for different routes of exposure. Since individuals are often exposed to a chemical by more than one route, separate route-specific HQ values are calculated. For example, the estimated inhalation dose would be divided by the SHD for inhalation to calculate an HQ for inhalation, while the estimated dose received from dermal contact would be divided by a dermal SHD to derive the HQ for this route of exposure. Typically, the HQ values for each relevant route of exposure are summed to derive a hazard index (HI) for that chemical. Interpretation of the HI is analogous to the HQ—values less than one indicate that the safe dose has not been exceeded (in this case, by the aggregate from all exposure routes). A value greater than one suggests that effects are possible, although not necessarily likely. The HI is also a means by which effects of different chemicals with similar toxicities can be combined to provide an estimate of total risk to the individual.

Another means to convey the relationship between estimated and safe levels of exposure is through calculation of a margin of exposure. This is most often used in the context of the BMD approach. The margin of exposure is the BMD divided by the estimated dose. An acceptable margin of exposure is usually defined by the uncertainty factors applied to the BMD. If, for example, available data suggest that a total uncertainty factor of 1000 should be applied to the BMD for a specific chemical and effect, and the margin of exposure for that chemical is greater than 1000 (i.e., the estimated dose is less than the BMD divided by 1000), the exposure would be regarded as safe.

A Special Case: Assessing Risk from Lead Exposure

The aforementioned methods are almost universally applied in assessing the potential for noncancer health effects. There is, however, one exception for which a radically different approach is used: the evaluation of noncancer effects from lead in children. In 2012, the Centers for Disease Control and Prevention (CDC) recommended blood lead concentrations in children should not exceed 5 μg/dl in order to avoid intellectual impairment (this is a decrease from their previous recommendation of 10 μg/dl). Thus, the main objective in lead risk assessment is to determine whether childhood lead exposure is sufficient to result in a blood lead level that causes adverse effects.

To predict blood lead levels from environmental exposure, the U.S. EPA has developed a PBPK model known as the "integrated exposure uptake biokinetic model for lead in children" (IEUBK). The IEUBK model has four basic components (i.e., exposure, uptake, biokinetics, and probability distribution) and uses complex mathematics to describe age-dependent anatomical and physiological functions that influence lead kinetics. The model predicts the blood concentration (the dose metric most closely related to the health effect of interest) that results from an endless variety of exposure scenarios that can be constructed by the risk assessor (i.e., exposure to various concentrations of lead in soil, dust, water, food, and/or ambient air). The model also predicts the probability that children exposed to lead in environmental media will have a blood lead concentration exceeding a health-based level of concern (see Figure 23.4). It is important to note that the U.S. EPA has not yet decreased their health-based level of concern and currently utilizes 10 μg/dl as specified in the 1994 *Revised Interim Soil Lead Guidance for CERCLA Sites and RCRA Corrective Action Facilities.* However, the IEUBK model allows the user to choose the blood lead level of concern. The IEUBK approach is rather unique because it is among the few approaches that

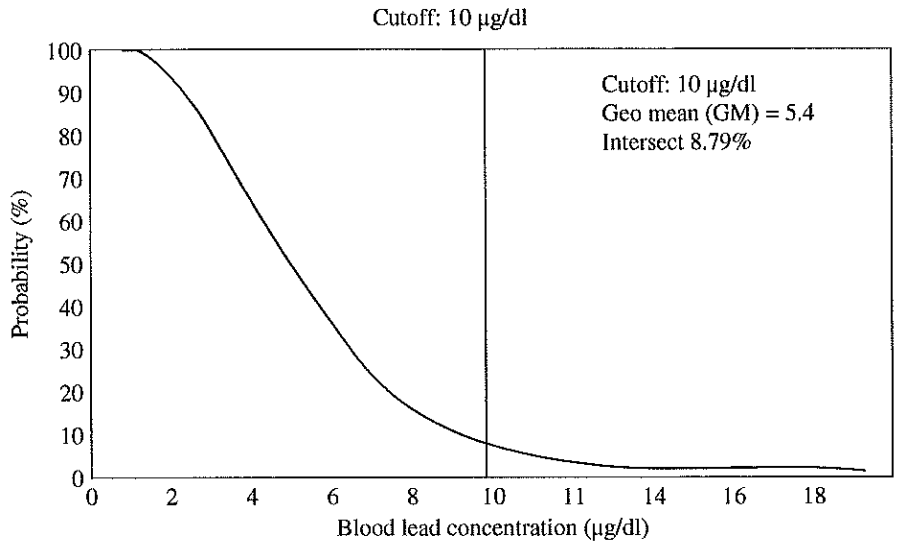

FIGURE 23.4 Example of output from the IEUBK model. The curve displays the cumulative probability of developing a blood lead concentration at varying media concentrations as a result of the specified exposure. In this example, there is a probability of virtually 100% that the modeled exposure will result in a blood lead concentration greater than 1 µg/dl, but only about a 9% probability that the blood lead concentration will exceed 10 µg/dl.

rely on an internal dose metric (i.e., blood lead level) and PBPK modeling for risk assessment purposes.

Nonthreshold Models for Assessing Cancer Risks

Conceptual Issues The nonthreshold dose–response model is typically reserved for cancer risk assessment. The assumption by regulatory agencies that chemical carcinogenesis has no dose threshold began several decades ago. This assumption was initially based largely on empirical evidence that radiation-induced cancer had no threshold and on the theory that some finite amount of DNA damage was induced by all doses of radiation. Smaller doses simply carried smaller risks, but all doses were assumed to carry some mathematical chance of inducing cancer. Following this lead, theories of chemical-induced carcinogenesis began to evolve along the same lines, centering on effects of highly reactive, DNA damaging carcinogens. It was presumed that, like radiation, chemical carcinogens induced cancer via mutations or genetic damage and therefore had no thresholds. So, like radiation before it, chemical-induced carcinogenesis was assumed to carry some quantifiable risk of cancer at any dose.

If viewed somewhat simplistically, a biologic basis for the absence of a practical threshold for carcinogens can be hypothesized. If one ignores the DNA repair processes of cells, or assumes that these protective processes become saturated or overwhelmed by "background" mutational events, it can be postulated that some unrepaired genetic damage occurs with each and every exposure to a carcinogenic substance. As this genetic damage is presumed to be permanent and carry the potential to alter the phenotypic expression of the call, any amount of damage, no matter how small, might carry with it some chance that the affected cell will ultimately evolve to become cancerous.

With this viewpoint, scientists and regulatory agencies initially proposed that the extrapolation of a cancer hazard must be fundamentally different from that used to extrapolate noncancer hazards, and cancer risk assessment models become probability based. In contrast to assessing the risk of noncancer health effects, where the dose at which no toxic effect will occur is determined, cancer risk assessment is a matter of assigning probabilities of cancer to different doses. The determination of safety or a safe dose is then a matter of deciding what cancer risks are so small that they can be regarded as de minimis or inconsequential.

Determining the relationship between carcinogen dose and cancer risk is very difficult for a number of reasons. One reason is that the concept of latency complicates the interpretation of dose–response relationships for carcinogens. *Latency* is the interval of time between the critical exposure and the ultimate development of disease. While noncancer effects tend to develop almost immediately or very soon after a toxic dose is received, cancer may not develop until an interval of 20 years or more has elapsed. For some carcinogens, increasing the dose shortens the latency period, causing tumors to develop more quickly. A positive carcinogenic response can then be thought of in two ways: as increased numbers of tumors or subjects with tumors or as a decrease in the time to appearance of tumors. The latter is important, because a dose capable of producing tumors has no consequence if the time required for the tumors to develop exceeds the remaining lifespan of a human or animal.

Another problem is that the critical portion of the dose–response curve for most risk assessments, the low-dose region applicable to most environmental and occupational exposures, is one for which empirical data are not available. Chronic cancer bioassays in animals are expensive and seldom test more than two or three doses. Also, cost limits the number of animals tested to about 50 or less per dose group. With this group size, only tumor responses of about 10% or more can be detected with statistical significance. Detection of the kinds of cancer responses that might be of interest to the risk assessor, for example, a response of 0.1, 0.001 or 0.00001% (10^{-3}, 10^{-5}, or 10^{-6}, respectively), is therefore beyond the capabilities of these experiments. Consequently, the doses needed to produce these cancer responses are not determined. Expanding the number of animals routinely tested is not economically feasible, and even very large studies may not eliminate this problem. One attempt to test the utility of using larger dose groups, the so-called "megamouse" experiment, was still unable to increase the sensitivity of measurement beyond about 1%, even though almost 25,000 animals were used in this experiment. In short, animal cancer bioassays will typically provide only one or two dose–response points, and these points are always several orders of magnitude above the range of small risks/doses in which we are ultimately interested.

Because low-dose responses cannot be measured, they must be modeled. There are three types of models:

1. The first category of models consists of the "mechanistic" models. These are dose–response models that attempt to base risk on a general theory of the biological steps that might be involved in the development of carcinogenesis. Examples of mechanistic models include the early "one-hit" and the subsequent "multihit" models for carcinogenesis. These models were based on assumptions concerning the number of "hits" or events of significant genetic damage that were necessary to induce cancer. A related model, the "linearized multistage" (LMS) model of carcinogenesis, is based on the theory that cancer cells develop through a series of different stages, evolving from normal cells to cancer cells that then multiply.
2. The second category of cancer extrapolation models includes the "threshold distribution" models. Rather than attempting to mimic a particular theory of carcinogenesis, these models are based upon the assumption that different individuals within a population of exposed persons will have different risk tolerances. This variation in tolerance in the exposed population is described with different probability distribution of the risk per unit of dose. Models that fall within this category include the probit, the logit, and the Weibull.
3. The third category of model is the "time-to-tumor" model. This type of model bases the risk or probability of getting cancer on the relationship between dose and latency. With this model, the risk of cancer is expressed temporally (in units of time), and a safe dose is selected as one where the interval between exposure and cancer is so long that the risk of other diseases becomes of greater concern.

Each of these models can accommodate the assumption that any finite dose poses a risk of cancer, the essential tenet of a nonthreshold model. However, the shape of the dose–response curve in the low-dose region can vary substantially among models (see Figure 23.5). Because the shape of the dose–response curve in the low-dose region cannot be verified by measurement, there is no means to determine which shape is correct. A simple example of the impact of choosing one cancer extrapolation model over another is given in Table 23.1, which compares the results of dose–response modeling using three different models where it was assumed in each model that a relative dose of 1.0 produced a 50% cancer incidence. The results generated by all three models are essentially indistinguishable at high doses where the animal cancer incidence might be observable, and so one would conclude that they all "fit" the experimental data equally well. However, when modeling the risks associated with lower doses, the dose/risk range in which regulatory agencies and risk assessors are most frequently interested,

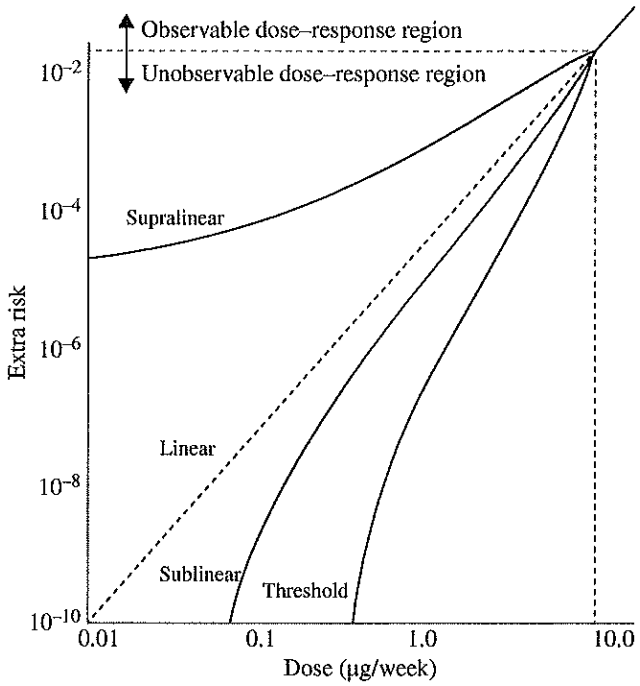

FIGURE 23.5 Four different extrapolation models applied to the same experimental data. All fit the data equally well in the observable range, but each yields substantially different risk estimates in the low-dose region most applicable to occupational and environmental exposures. *Source:* Adapted from NRC (1983).

TABLE 23.1 Expected Risk (Cancer Incidence) Calculated by Three Models when a Relative Dose of 1.0 Is Assumed to Cause a 50% Tumor Incidence in Test Animals

	Modeled Tumor Incidence (%)		
Relative Dose	Lognormal	Log-Logistic	One-Hit
16	98	96	100
4	84	84	94
1[a]	**50**[a]	**50**[a]	**50**[a]
1/4	16	16	16
1/16	2	4	4
1/100	0.05	0.4	0.7
1/1000	0.00035	0.026	0.07
1/10,000	0.0000001	0.0016	0.007

Source: Adapted from Office of Technology Assessment (1981).
[a]Boldface numbers represent the only data assumed for each model; all other tumor incidences were calculated from this single dose–response point.

there is a wide divergence in the risk projected by each model for a given low dose. In fact, at 1/10,000th of the dose causing a 50% cancer incidence in animals, the risks predicted by these three models produce a 70,000-fold variation in the predicted response.

Regulatory agencies utilize cancer risk estimates in regulating carcinogens, but they are faced with many models that yield a wide range of risk estimates. In the absence of any scientific basis to determine which is most correct, they must make a science policy decision in selecting the model to use. Generally, in the face of this uncertainty, they have selected models that tend to provide higher estimates of risk particularly when combined with conservative exposure assumptions (see Table 23.2). This is consistent with their mission to protect public health, and consequently the need to avoid underestimating risks. For example, the U.S. EPA has historically used conservative models such as the one-hit of LMS model in calculating cancer risks from exposure to all carcinogens. These models assume linearity in the low-dose range and, as shown in Table 23.1, tend to require a larger reduction in dose to attain a certain low level of risk relative to other models.

Extensive research in the area of chemical carcinogenesis indicates that many chemical carcinogens act via epigenetic or promotional mechanisms that, like noncancer toxicities, do not involve or require genetic damage. It has been proposed that these mechanisms and carcinogenic responses should have thresholds. Similarly, numerous enzyme systems have been identified as responsible for maintaining the integrity of the genetic code. These repair enzymes and pathways could provide an effective dose threshold for even those carcinogens whose mechanism is believed to involve some mutational event or other form of genetic damage.

In recent years, debates involving the actual shape of the dose–response curve for carcinogens in the low-dose region, and the issue of thresholds for carcinogens, have caused scientists and regulatory agencies to reevaluate

TABLE 23.2 The Estimated Impact of Six Conservative U.S. EPA Assumptions on Agency Risk Assessments

Factor	Range of Possible Overstatement of Estimated Cancer Risk[a]
Body weight versus surface area as a scalar for an interspecies extrapolation	2–12
MLE[b] versus 95% UCL[c] for the cancer slope factor	1–3
Malignant tumors only versus malignant + benign	1–2
Average species sensitivity versus most sensitive species	2–5
Pharmacodynamics versus effective dose	1–6
Risks at shorter than equilibrium buildup time	2–5
Total risk exaggeration	15–10,800

Source: Adapted from Barnard (1994) and based on information supplied by Dr. E. Anderson.
[a]Instead of presenting ranges of possible overstatement in cancer risk, the Barnard paper presents ranges of possible reduction in estimated cancer risk if the alternative factors to the current default factors are applied.
[b]Maximum likelihood exposure.
[c]Upper confidence limit.

earlier cancer risk assessment methodologies. Out of this reevaluation has come a movement to adopt two major policy changes in the cancer risk assessment methodologies employed by regulatory agencies. One proposed change is to use risk extrapolation models that make fewer assumptions about the shape of the dose–response curve (e.g., the BMD and margin-of-exposure method). Data within the observation range can be used to develop a "point of departure," the critical point for extrapolating responses in the low-dose range. For dose–response relationships assumed to have no threshold, the simplest extrapolation model is used: a straight line drawn between the point of departure and zero. The second proposed change is to allow for the consideration and use of nonlinear and threshold models for carcinogens where empirical and mechanistic evidence argues strongly that this type of dose–response model is appropriate for a particular chemical. In this situation, risk of cancer would be evaluated in a manner analogous to noncancer health effects, such as through calculation of a margin of exposure.

Generating Cancer Risk Estimates Estimating the lifetime cancer risk associated with a particular dose is a relatively simple mathematical process. Because most regulatory agencies such as the U.S. EPA use the conservative assumption that cancer risk should be modeled via a linear, nonthreshold

model, the risk associated with a particular dose is calculated by the following formula:

$$R = D \times \text{CSF} \quad \text{or} \quad R = \text{LADD} \times \text{CSF}$$

where

R = risk,

D = dose (normally expressed as the lifetime average daily dose (LADD) (mg/kg · day)), and

CSF = cancer slope factor (the slope of the dose–response curve in units of $(\text{mg/kg} \cdot \text{day})^{-1}$).

With this equation, the total dose the individual or population has accumulated during their entire exposure interval is first converted into a LADD, a dose that if received every day for a lifetime would be equivalent to the total dose accumulated during the actual exposure period. For example, if the exposure assessment projected a daily dosage of 70 mg/kg · day for a 30-year exposure interval, then the LADD assuming a 70-year lifespan would be 30 mg/kg · day (i.e., 70 mg/kg · day × 30 years ÷ 70 years = 30 mg/kg · day). The dose is expressed in units of mg/kg · day, and the CSF is in units of reciprocal mg/kg · day or $(\text{mg/kg} \cdot \text{day})^{-1}$. If the chemical in this example has a CSF of 0.001 $(\text{mg/kg} \cdot \text{day})^{-1}$ (in scientific notation a value of 1.0×10^{-3} $(\text{mg/kg} \cdot \text{day})^{-1}$) and the LADD derived during the exposure assessment was 0.03 mg/kg · day (3.0×10^{-2} mg/kg · day), the risk would be as follows:

$$R = 0.001\,\text{mg/kg day} \times 0.03\,(\text{mg/kg day})^{-1} = 0.00003$$

Which can also be written as

$$R = \frac{3}{100{,}000} \quad \text{or} \quad R = 3.0 \times 10^{-5}$$

In this example, the risk estimate represents a 3/100,000 chance or mathematical probability that a cancer will develop from exposure. It should also be noted, however, that because regulatory agencies strive for conservative, health-protective risk calculations, the CSF used is statistically an upper-bound estimate of the dose–cancer relationship. The true cancer risk of the chemical at this dose may be much less than that calculated and, in fact, could be as low as zero.

Dose Metrics

A common issue for both threshold and nonthreshold dose–response relationships is the metric used to express dose. The dose metric is important because animal data must often be used as a surrogate for dose–response information in humans. Humans are, of course, much different in size than most laboratory animals. How then should doses be scaled between one animal species and another, and between animals and humans?

One can improve the accuracy of SHD calculations by starting with the best "dose metric" (measure of the dose) for the actual amount of chemical required to induce toxicity in the most sensitive target organ. Most dose information in animal studies is reported in terms of the "applied dose" (the dose administered to the whole animal). Remember, however, that it is only the "absorbed dose" (the amount of the chemical actually absorbed into the body) that is eligible for inducing toxicity. Further, from the dose that is absorbed, it is the dose that reaches the target tissue that is most important in determining the extent of response. The relationship between applied dose and target organ dose can be different among species, due to differences in metabolism and/or distribution of the chemical within the body, leading to important differences in apparent dose–response relationships (i.e., those based strictly on applied dose). One approach used to enhance extrapolation among species is PBPK modeling. Using PBPK models, scientists are able to predict target organ doses of a chemical (or a critical metabolite, if that is important for toxicity) in test species and humans. With this information, corrections can be made for pharmacokinetic differences among species, leading to better extrapolation of dose–response relationships. The principal limitation of PBPK analyses is that they are data intensive, and PBPK models have been constructed and validated for only a few chemicals (see Chapter 3).

Since PBPK models are not often available, simpler approaches to extrapolating doses must be used in most situations. One of the simplest approaches is to convey doses per unit body weight. Larger animals (or humans) are assumed to require larger doses to produce the same toxic effect in proportion to their body weight. This is the dose metric most commonly used when extrapolating information on health effects among species. In biology, empirical observations suggest that many biochemical and physiological processes seem to scale among species according to surface area, while differences in others seem to correspond more closely to changes in weight. The correct scaling for doses is not entirely obvious and could conceivably be different for different chemical classes or toxicological effects. The current recommendation from the U.S. EPA is that scaling for both noncarcinogen and carcinogen doses uses a factor intermediate between body weight (or body weight raised to the power of 1) and surface area (body weight raised to the power of 0.67); that is, body weight raised to the power of 0.75.

Does the choice of scaling factor really make a difference? To illustrate the answer, consider the extrapolation of dose information between a mouse and a human. If a dose for a noncancer effect in a mouse were converted to a human dose based on surface area, rather than on body weight, the SHD dose would be reduced by a factor of 12 to 14. On the other hand, switching from surface area scaling to body weight

scaling for carcinogenicity data would result in a 12- to 14-fold decrease in cancer risks estimated from the same dose–response information. The difference in use of body weight versus surface area for extrapolating between rats and humans is not as large (about six-fold), but still might be considered significant.

23.4 EXPOSURE ASSESSMENT: EXPOSURE PATHWAYS AND RESULTING DOSAGES

Exposure assessment can be defined as the measurement or estimation of the amount or concentration of a chemical(s) coming into contact with the body at potential sites of entry (e.g., skin, lung, GI tract). Not only are the amount and route of exposure concerns, but so too are the exposure duration, exposure frequency, and any factors that modify the ability of the chemical to traverse the portals of entry into the body. In cases where a potential chemical hazard exists, exposure assessment is an obligatory part of the risk assessment process. Without exposure, even the most hazardous chemical poses no risk. Conversely, excessive exposure to minimally hazardous chemicals may pose an unacceptable risk. Therefore, risk assessment requires that toxicity and exposure assessments be coupled. Initially, exposure assessments should identify all potential exposure pathways and assess their completeness, after which the quantification of exposure via each relevant pathway should be determined.

Exposure pathways consist of four basic parts: (1) source of contamination, (2) contaminated media, (3) contact with the contaminated media, and (4) a route of exposure. All of these parts must be present to produce an exposure. If one of these parts is absent, there is no exposure and no risk. Soil, sediment, groundwater, surface water, air, dust, and biota may all function as the contaminated media. They become contaminated directly by a chemical release or indirectly by contact with another contaminated media. Exposure pathways are usually illustrated in the conceptual site model (CSM). The CSM is a visual representation of the complete and incomplete exposure pathways at a release. Depending on the complexity of the CSM, exposure routes may also be represented. The main exposure routes include ingestion, dermal absorption, and inhalation (both vapors and particulates).

There are two basic methods for quantifying exposure: exposure measurement and exposure modeling. Measurement results in the most accurate and realistic exposure data, but fully characterizing variable exposures that might occur to multiple receptors via multiple pathways for an extended period of time is seldom feasible. In general, the measurement of occupational exposure is easier than environmental exposure, since the former usually occurs in a confined facility, whereas the latter involves more complex time–activity patterns. Also, occupational exposure limits are typically based on 8 h time-weighted averages and 15 min short-term exposure limits, making monitoring for compliance purposes manageable from a time standpoint. Examples of personal exposure measures include analyzing a person's intake of food and water and the contaminants therein, collecting and analyzing a urine sample at the end of a work shift, and measuring airborne exposure with a portable sampling device suspended in a person's breathing zone. Where environmental exposure to a large population is at issue, personal exposure monitoring is not a realistic approach. Rather, environmental media suspected of being contaminated are sampled and population-based assumptions about intake rates are made. Personal questionnaires and time–activity logs are helpful in making accurate exposure estimates within a large population.

In those cases where monitoring data are unavailable or inadequate for exposure assessment, models are used to simulate the behavior of chemicals and predict their concentrations in the environment. Hundreds of such exposure models exist, including atmospheric models, surface water models, groundwater models, and food chain models. All of these models are limited by uncertainty in the data input, as well as uncertainty to the predictive capability of a generic model for a specific exposure scenario. In recognition of this uncertainty, models used for regulatory purposes tend to provide liberal estimates of exposure that may overstate risk. Whenever models are used, an attempt should always be made to collect site- or situation-specific data for the purpose of model validation. Despite their limitations, exposure models are of value in that they can make predictions for an unlimited number of exposure scenarios and predict past and future exposures. Exposure measurement, on the other hand, is limited to the present.

Exposure or concentration is often expressed in units of $\mu g/m^3$ (air), $\mu g/l$ (water), or $\mu g/cm^2$ (skin). Air and water concentrations are also frequently reported in parts per million (ppm) or parts per billion (ppb) units that reflect the weight or volume of chemical per unit volume of the carrier medium. For some chemicals, risk can be directly calculated from these concentration terms using unit risk factors that are expressed as risk per $\mu g/l$ (water) or risk per $\mu g/m^3$ (air). In such cases, risk is simply the product of the chemical concentration and the unit risk factor. Exposure or concentration data can also be directly compared to many occupational (e.g., OSHA permissible exposure limits (PELs) and the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs®)) and environmental (U.S. EPA Maximum Contaminant Levels [MCLs], National Ambient Air-Quality Standards [NAAQS], and RfCs) exposure standards that have risk considerations inherent in their derivation.

While some exposure to a hazardous chemical is required in order to have risk, it is dose that relates more closely to the toxic response. Dose, often expressed in units of mg/kg body weight · day, is the amount of chemical that is either absorbed or available to be absorbed into the body where it can interact

with the target tissue (liver, thyroid, red blood cells, etc.). Knowledge of the exposure or concentration of a chemical is essential to determine the magnitude of the dose received. So, too, is knowledge of certain exposure factors such as the volume of contaminated air inhaled or food and water ingested per unit time. In fact, in many cases, it is quite simple to calculate dose when exposure concentration and exposure rate are known. To assist the risk assessor in making dose calculations, the U.S. EPA has published equations that are applicable to a variety of the most frequently encountered exposure scenarios. These equations, including the ones used below, are found in the document entitled *Risk Assessment Guidance for Superfund (RAGS), Human Health Evaluation Manual Part A (U.S. EPA, 1989)*. The following section provides example dose equations for some common exposure pathways:

Inhalation

$$\text{Dose}\,(\text{mg/m}^3) = \frac{\text{CA} \times \text{EF} \times \text{ED} \times \text{ET}}{\text{AT}}$$

where
CA = chemical concentration in air (mg/m^3),
EF = exposure frequency (days/year),
ED = exposure duration (years),
ET = exposure time (hours/day) × 1/24 day/hours, and
AT = averaging time (days).

Should it be desirable to express the safe air concentration in parts of toxicant per million parts of air, the dose (where the air concentration is in units of milligrams per cubic meter of air [mg/m^3]) may be converted to a ppm level by the following relationship:

$$\text{ppm} = \frac{\text{Dose}\,(\text{mg/m}^3) \times 24.5}{\text{MW}}$$

where MW is the molecular weight of the chemical (g/mol) and 24.5 is the amount (liters) of vapor per mole of contaminant at 25 °C and 760 mm Hg.

Ingestion of Groundwater

$$\text{Dose}\,(\text{mg/kg} \cdot \text{day}) = \frac{\text{CW} \times \text{IR} \times \text{EF} \times \text{ED}}{\text{BW} \times \text{AT}}$$

where
CW = chemical concentration in water (mg/l),
IR = ingestion rate (l/day),
EF = exposure frequency (days/year),
ED = exposure duration (years),
BW = body weight (kg), and
AT = averaging time (days).

Ingestion of Soil

$$\text{Dose}\,(\text{mg/kg} \cdot \text{day}) = \frac{\text{CS} \times \text{IR} \times \text{RBA} \times \text{EF} \times \text{ED}}{\text{BW} \times \text{AT}}$$

where
CS = chemical concentration in soil (mg/kg),
IR = ingestion rate (kg/day),
RBA = chemical-specific relative bioavailability,
EF = exposure frequency (days/year),
ED = exposure duration (years),
BW = body weight (kg), and
AT = averaging time (days).

Dermal Contact with Water

$$\text{Absorbed dose}\,(\text{mg/kg} \cdot \text{day}) = \frac{\text{CW} \times \text{SA} \times \text{PC} \times \text{ET} \times \text{EF} \times \text{ED} \times \text{CF}}{\text{BW} \times \text{AT}}$$

where
CW = chemical concentration in water (mg/l),
SA = skin surface area available for contact (cm^2),
PC = chemical-specific dermal permeability coefficient (cm/h),
ET = exposure time (hours/day),
EF = exposure frequency (days/year),
ED = exposure duration (years),
CF = conversion factor (1 l/1000 cm^3),
BW = body weight (kg), and
AT = averaging time (days).

Dermal Contact with Soil

$$\text{Absorbed dose}\,(\text{mg/kg} \cdot \text{day}) = \frac{\text{CW} \times \text{SA} \times \text{AF} \times \text{DA} \times \text{EF} \times \text{ED} \times \text{CF}}{\text{BW} \times \text{AT}}$$

where
CS = concentration in soil (mg/kg),
SA = skin surface area available for contact (cm^2/day),
AF = adherence factor for soil (mg/cm^2),
DA = dermal absorption,
EF = exposure frequency (days/year),
ED = exposure duration (years),
CF = conversion factor (10^{-6} kg/mg),
BW = body weight (kg), and
AT = averaging time (days).

To illustrate dose calculation, assume that a 16 kg child ingests 200 mg soil/day containing 400 mg/kg of chemical X, a volatile solvent. As shown in the following example, the child's dose of chemical X from the ingestion of soil is 1.25×10^{-3} mg/kg · day. This figure may not represent total dose, however, since dermal and/or inhalation exposure to the volatile chemical is likely. This illustrates the importance of considering all exposure pathways when assessing exposure

for the purpose of risk assessment. Failing to do so may result in the underestimation of risk.

The following formula can be used to determine the residential exposure from ingestion of a chemical in soil by a 5-year-old child receptor:

$$\text{Dose}(\text{mg/kg}\cdot\text{day}) = \frac{\text{CS}\times\text{IR}\times\text{CF}\times\text{FI}\times\text{EF}\times\text{ED}}{\text{BW}\times\text{AT}}$$
$$= \frac{400\text{mg/kg}\times 200\text{mg/day}\times 10^{-6}\text{kg/mg}\times 0.25\times 365\text{days/year}\times 6\text{years}}{16\text{kg}\times 2190\text{days}}$$
$$= 1.25\times 10^{-3}\text{mg/kg}\cdot\text{day}$$

where

CS = chemical concentration in soil (mg/kg) = 400 mg/kg (site-specific value),

IR = ingestion rate (mg soil/day) = 200 mg soil/day (default value for children 1–6 years old),

CF = conversion factor (10^{-6} kg/mg),

FI = fraction ingested from contaminated source (unitless) = 0.25 (site-specific value),

EF = exposure frequency (days/year) = 365 days/year (site-specific value),

ED = exposure duration (years) = 6 years (site-specific value),

BW = body weight (kg) = 16 kg (default value for children 1–6 years old), and

AT = averaging time (period over which exposure is averaged in days) = 6 years × 365 days/year = 2190 days for noncancer effects.

As shown in this example, where the intake of chemical X from soil ingestion was calculated for a 5-year-old child, default values for input variables can be used where site-specific data are lacking. The most complete collection of default values has been compiled and published by the U.S. EPA as the *Exposure Factors Handbook* (2011) and the *Child Exposure Factors Handbook* (2008). Numerous distributions (vs. discrete values) for input variables used in exposure calculations have also been reported that are of value to probabilistic risk assessment. In addition, the U.S. EPA has published several guidance documents that address many of the issues related to characterizing exposures for selected pathways:

- *Guidelines for Exposure Assessment* (USEPA, 1992)
- *Risk Assessment Guidance for Superfund* (USEPA, 1989)
- *A Framework for Assessing Health Risk of Environmental Exposures to Children* (USEPA, 2006)
- *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (USEPA, 2005)
- *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin and Related Compounds, National Academy Sciences (External Review Draft)* (USEPA, 2004)
- *Guidance Document on the Development, Evaluation, and Application of Environmental Models* (USEPA, 2009)
- *Standard Scenarios for Estimating Exposure to Chemical Substances During Use of Consumer Products* (USEPA, 1986)
- *Available EPA Information on Assessing Exposure to Pesticides in Food: A User's Guide* (USEPA, 2000)
- *Standard Operating Procedures for Residential Pesticide Exposure Assessment* (USEPA, 2012)
- *Framework for Cumulative Risk Assessment* (USEPA, 2003)

Once dose has been estimated for all exposure pathways, it can be directly compared to toxicity values such as U.S. EPA RfDs and Agency for Toxic Substances and Disease Registry minimal risk levels (MRLs) to assess noncancer risks or, alternatively, multiplied by cancer slope factors to obtain an estimate of cancer risk. Another word of caution is in order, however. Toxicity values, including cancer slope factors, may be specific for particular exposure routes (MRLs vary by exposure route and exposure duration) since target organ dose and, for some chemicals, the target organ itself can be exposure route dependent.

While the administered dose and absorbed dose are common dose measures, they do not reflect the amount of the chemical or its metabolite(s) that ultimately produces the toxic response (except in cases where chemicals exert their action locally, as in the case of strong acids or bases that produce dermatotoxicity on contact). The toxic response is more closely linked to the dose in the target tissue of interest (see Figure 23.6 for a schematic showing the relationships between exposure and various dose measures). For example, solvent-induced neurobehavioral toxicity may be a function of peak brain concentration of the parent compound, whereas liver toxicity from the same chemical may be related to the hepatic tissue concentration of one or more metabolites over time (called the *area under the tissue concentration-time curve* (AUC)). The identification of such internal dose measures that are mechanistically linked to various toxicities holds promise for improving the risk assessment process. It is commonly assumed in interspecies extrapolation that the target tissue dose required to produce a biological effect of a given intensity is quantitatively similar across species. Therefore, dose–response curves generated with measures of target tissue dose should be more extrapolatable across

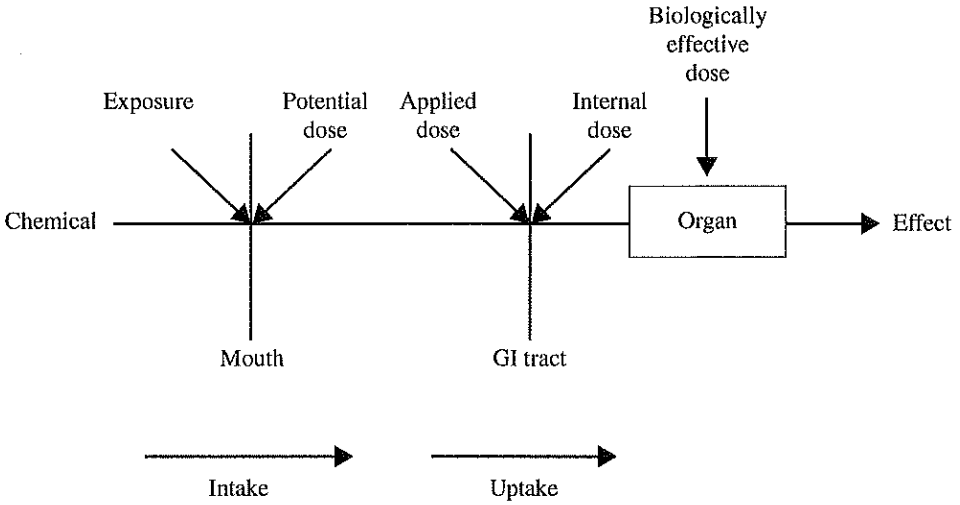

FIGURE 23.6 The relationship between exposure and various measures of dose. *Source:* Adapted from USEPA (1997).

species since they obviate the need for consideration of interspecies differences in the toxicokinetics of an administered dose. Unfortunately, dose–response curves of this nature are rare, primarily because of the technical difficulties inherent in internal dose measurement. This is likely to change, however, as advancements are made in analytical chemistry and PBPK models find their way into the mainstream. Such models are powerful tools with which to estimate internal dose measures from an endless variety of exposure scenarios to physiologically diverse receptors. As such, they are particularly valuable for the purpose of interspecies extrapolation (see Chapter 3).

Biological monitoring is another means of exposure assessment. When it is conducted to measure a chemical or its metabolites in the urine, blood, or tissue (including hair and fingernails) of an exposed individual, the chemical and its metabolites are referred to as *biomarkers of exposure*. Other potential biomarkers include DNA and protein adducts, mutations, chromosomal aberrations, genes that have undergone induction, and a host of other "early" cellular or subcellular events thought to link exposure and effect. The characterization and quantification of these latter biomarkers is known as *molecular dosimetry*. If found to be correlated with susceptibility, exposure, and effect, these biomarkers could considerably alter conventional approaches to risk assessment. Perhaps the best known example of such a correlation is urinary aflatoxin–DNA adducts and liver cancer. While molecular dosimetry holds promise for risk assessment, it is yet to be developed well enough for routine application.

Despite advancements in analytical chemistry, mathematical modeling, and biomonitoring, exposure assessment remains a challenge. It is important to realize that most exposure assessments result in estimates rather than definitive values. This stems in part from the fact that site- or situation-specific values are rarely available for all of the input variables necessary to calculate exposure. Despite the challenge, efforts should continue toward conducting exposure assessments that reflect realistic exposures. The identification of the dose metric that best correlates with various toxicities should also be a priority. Since this depends on a thorough knowledge of a chemical's mode of action, advancement in exposure assessment is inextricably linked to advances in toxicology.

23.5 RISK CHARACTERIZATION

The purpose of the risk characterization step is to integrate information provided by the hazard identification, dose–response assessment, and exposure assessment in order to develop risk estimates. Risk information may be conveyed in a qualitative manner, quantitative manner, or both. A qualitative assessment may describe the hazard posed by chemicals of concern, discuss opportunities for exposure, and reach some general conclusions that the risks are likely to be high or low, but would not provide numerical estimates of risk. A quantitative risk characterization, on the other hand, includes numerical risk values. Theoretically, there are many ways that numerical risks could be calculated depending on the specific questions being addressed in the risk assessment. For example, risks could be expressed as an individual's excess lifetime risk of developing a particular health effect as a result of chemical exposure. Risks could also be expressed on a population basis (e.g., estimated number of extra cases of a disease per year attributable to chemical exposure) or as the relative risk of an exposed population versus an unexposed population. Other ways of expressing risks, or health impacts, could be in terms of loss of life expectancy or lost days of work.

As discussed in Section 23.3, the most common means of expressing cancer risk associated with chemical exposure is in the form of individual excess lifetime cancer risk. When calculated for regulatory purposes, these values are intended to represent upper-bound estimates. That is, a cancer risk of one in one million means that an individual chosen at random from the exposed population is likely to have a probability no greater than one in one million of developing cancer as a result of that exposure. Note that this is an excess probability of developing cancer associated specifically with the chemical exposure addressed in the risk assessment, not the overall probability of developing cancer. The risk assessment provides an estimate of excess cancer risks, but does not determine whether the excess cancer risks are acceptable or unacceptable. That determination lies in the province of risk management, which must balance the risk estimate with other considerations (e.g., likelihood of actual exposure, uncertainties in the risk estimate, costs and feasibility of risk reduction strategies) to make decisions regarding steps, if any, to be taken to address chemical exposures. In some situations, an excess cancer risk of 1×10^{-3} (one in one thousand) from chemical exposure has been acceptable to regulatory agencies, while in others, any excess risk above 1×10^{-6} (one in one million) has been deemed too high. Travis et al. (1987) reviewed the risks associated with 132 federal regulatory decisions involving environmental carcinogens to determine the level of risk that led to regulatory action. Their analysis revealed that with large populations an action was always taken when the risk exceeded 10^{-4}. For small populations, historically, the *de manifestis level*, that is, the level at which action is always taken, was a risk of 10^{-3}. The *de minimis risk level* for these 132 regulatory actions, namely, the level of risk where no action or consideration is deemed necessary, was 10^{-5} to 10^{-4} for small populations and 10^{-6} to 10^{-7} for large populations. Others have suggested that the risk to smaller populations (e.g., a specific workforce) may be justifiably higher as long as the projected risk does not result in the expectation of an additional cancer. For example, if 100 persons were exposed to a 10^{-3} lifetime risk, the total population risk would be only 0.1, and an additional cancer case would be unlikely. The range of "acceptable risks" that has been applied by the U.S. EPA across its various regulatory programs seems to support the conclusions of the regulatory analysis performed by Travis and coworkers. The acceptable risk ranges of several U.S. EPA programs are:

- 10^{-4} to 10^{-6}: the cleanup policy under the U.S. EPA Superfund Cleanup Program of the National Oil and Hazardous Substances Pollution Contingency Plan
- 10^{-4} to 10^{-6}: U.S. EPA drinking water standards (MCLs) under the Safe Drinking Water Act
- 10^{-2} to 10^{-6}: National Emission Standards for Hazardous Air Pollutants (NESHAPs) under the Clean Air Act
- 10^{-4} to 10^{-6}: for corrective actions under the Resource Conservation and Recovery Act

For carcinogens with thresholds, risk is portrayed as a margin of exposure. (*Note:* The concept of margin of exposure is discussed in Section 23.3.) Just as the definition of an acceptable cancer risk in probability terms is outside the scope of the risk assessment, an acceptable margin of exposure is essentially a policy and risk management issue. The margin-of-exposure concept is also applicable to noncancer effects and is used to convey the difference between the estimated exposure to a chemical and the BMD, usually for the most sensitive effect. The other, more common, means of expressing hazard for noncancer effects is the HI. By convention, an HI greater than 1 signals concern for the possibility of adverse effects. The likelihood that health effects will actually occur with an HI greater than 1 depends in part on the chemicals in question and the margin of safety inherent in the toxicity values used to calculate the HI. These issues bear discussion in the risk characterization, so as to better inform the risk management decisions.

During the risk characterization step, risks from various chemicals, reaching individuals by various pathways and conceivably entering the body by various routes, must be combined in some way such that the total risk to individuals from chemical exposure can be assessed. Methods for combining risks are discussed in Section 23.7. It is not uncommon for risk estimates to be presented for a number of different populations. This may include groups of individuals exposed in different ways (e.g., workers at a contaminated site vs. visitors to the site vs. residents living nearby the site) or individuals that may differ in their sensitivity to hazards posed by the chemicals of concern (e.g., children, pregnant women). Development of these various risk estimates is important, not only in providing a complete characterization of potential risks posed by the chemicals but also in developing effective strategies for managing the risks.

A particularly important aspect of the risk characterization is a discussion of the uncertainties associated with the risk estimates. Each individual step in the risk assessment process is a potential source of uncertainty. Many of these are discussed throughout the chapter and include uncertainty associated with estimating exposure (e.g., measurement errors, uncertainty in selecting the best exposure models, uncertainty regarding exposure conditions that will exist in the future) as well as determining safe levels of exposure (e.g., uncertainty regarding the shape of the dose–response relationship in the low-dose region and extrapolating results from animals to humans, uncertainty that the most sensitive health effect has been identified, uncertainty regarding ways that multiple chemicals might interact). These need to be articulated in the risk characterization so that an appreciation of the level of confidence and conservatism in the risk estimate can be gained. Without a discussion of uncertainty, risk assessment results are often perceived as being more precise than they really are, which could lead to misuse. Minimally, uncertainties should be discussed qualitatively,

identifying the source or nature of each uncertainty and how, in a general way, it could affect the risk estimation (i.e., whether the approach taken, in view of the uncertainty, is likely to contribute to an over- or underestimation of risk). A semiquantitative perspective is helpful, in which the implications of model and assumption choices on the risk estimate are described in rough, order-of-magnitude terms. As discussed in Section 23.6, probabilistic techniques can be used to provide more precise quantitative expression of the uncertainties associated with risk estimates, as well as a description of variability in risks encountered in exposed populations. This approach is attractive in that it offers a much richer characterization of the risks and uncertainties than do the more traditional risk estimation techniques. It is technically demanding, however, requiring much greater time, resources, data, and technical expertise.

23.6 PROBABILISTIC VERSUS DETERMINISTIC RISK ASSESSMENTS

Risk assessments are rarely performed for a single individual. Instead, risk assessments are designed primarily to characterize risks to populations of individuals. Many—perhaps most—of the factors that affect risk can vary from one person to another. Differences in body weight, inhalation rate, frequency and duration of contact with contaminated media, and even sensitivity to toxicity are examples of factors that can lead to different risks among individuals, even if the concentration of chemical to which they are all exposed is the same. Theoretically, there is no single risk for a particular exposure circumstance, but rather as many different risk values as there are individuals in the exposed population. In confronting the issue of variability in risk assessment, the traditional approach used for regulatory purposes has been to simply characterize the risk to individuals within the population with the greatest exposure. A *deterministic approach* to risk calculation is used, where a single value is selected for each exposure variable and a single risk estimate is produced. The exposure assumptions are chosen to represent the plausible upper bound of exposure, and the risk estimate is said to be associated with reasonable maximal exposure (RME) or high-end exposure. The development of a single, high-end risk estimate for regulatory use is consistent with the goal of regulatory agencies to develop risk management strategies protective of the entire population. For perspective, a deterministic approach may also be used to develop an estimate of risk for the average individual in the population, that is, a central tendency estimate of the risk. The problem with this approach is that it provides little information on the extent to which risk varies within the population. For example, while exposure values may be selected to develop a high-end estimate of risk, it is difficult to know whether this value is merely conservative or extreme. Does it represent an exposure that might be exceeded by 1 or 2 out of every 10 individuals, or does it represent an exposure circumstance so extreme that it is unlikely ever to take place? This imprecision regarding the degree of conservatism in deterministic risk estimates undermines their value and creates controversy regarding their use in regulatory decision making.

A second problem confronting the risk assessor is management of uncertainty in the risk assessment process. As described elsewhere in this chapter, there are numerous sources of uncertainty in risk calculations, including uncertainty in the selection of models and assumptions and in measurements of risk-related parameters. As part of a deterministic calculation of risk, a choice must be made for each of these so that a risk estimate can be made. For regulatory purposes, conservative choices are usually made; models and assumptions that tend to provide higher estimates of risk are selected from among the range of plausible alternatives. The reason for conservative choices by regulatory agencies in the face of uncertainty is well understood, but the extent of conservatism imparted by the various choices is usually unclear. As with the issue of variability, this makes it difficult or impossible for the risk assessor to effectively convey the inherent conservatism associated with the risk estimate.

Probabilistic risk assessment is an alternative approach that can address the limitations of deterministic calculations in terms of variability and uncertainty. In probabilistic risk assessment, input variables are entered as probability density functions (PDFs) instead of single values. For example, instead of using a single body weight of 70 kg in the risk calculation, a distribution of body weights would be entered that reflects the variability in body weight of the exposed population. PDFs might also be entered for other variables such as inhalation rate, skin surface area, and frequency of contact with contaminated media—anything that would be expected to vary from one individual to another. These PDFs are then combined in such a way as to yield a risk distribution, representing the range and frequency of risks anticipated to exist in the exposed population. Although there are several ways to combine PDFs, one of the most commonly used techniques is Monte Carlo simulation. With Monte Carlo simulation, a computer program in essence creates a simulated population designed to resemble the exposed population in every key respect. For each risk calculation, it takes a value from each input PDF chosen in relation to its probability and calculates a numerical risk. This process is repeated, usually thousands of times, and the resulting range of risk values is tallied in the form of a distribution. This distribution represents the risk distribution for the population. From this distribution, the variability in risk among individuals can be visualized and the risk level at various percentiles of the population determined (see Figure 23.7).

Probabilistic risk assessment can also provide quantitative representation of the uncertainties in the risk calculation. For each input or model, some estimate of the uncertainty is

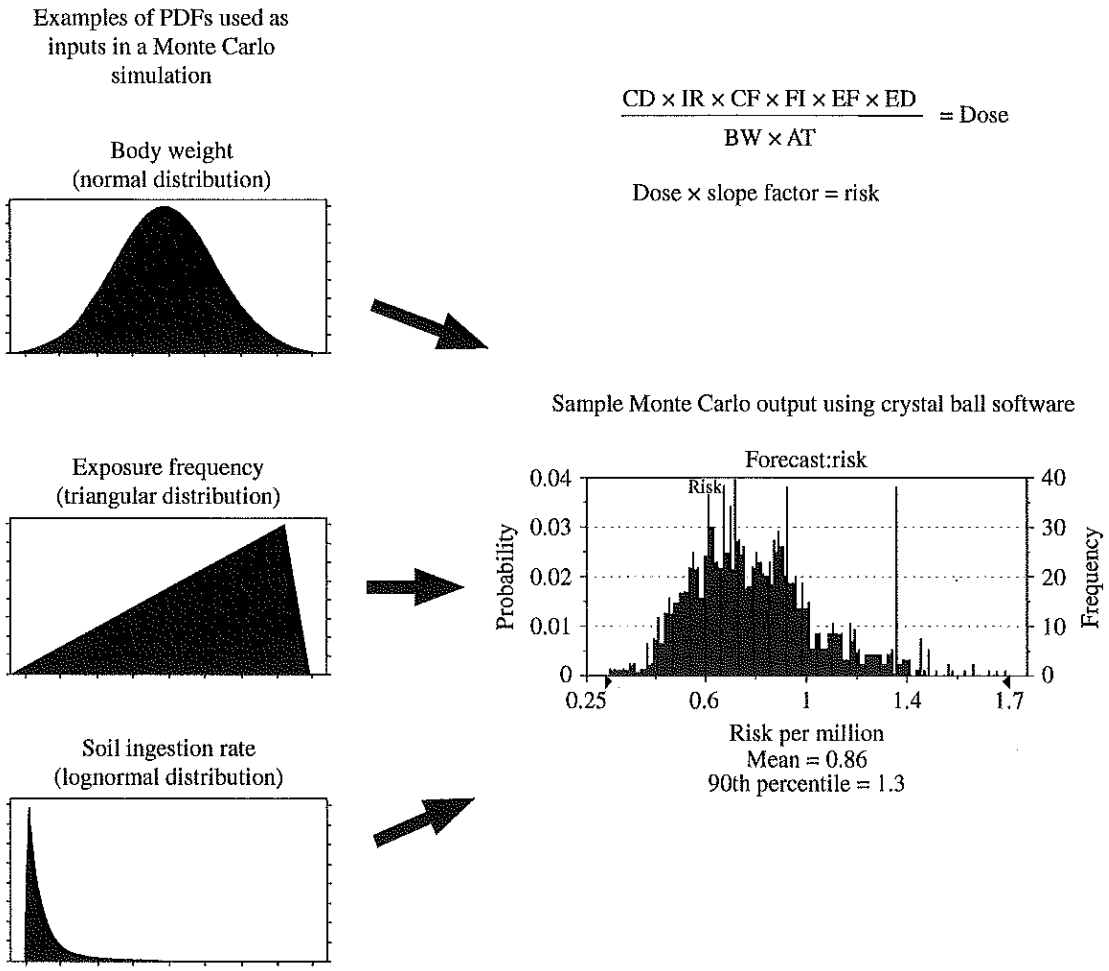

FIGURE 23.7 Simplified diagram of combining probability density functions (PDFs) to yield a risk distribution in probabilistic risk analysis. In this example, dose is calculated as described in Section 23.4, except each of the inputs for which variability exists is entered as a PDF. Examples of PDFs for body weight, exposure frequency, and soil ingestion rate are shown. Using Monte Carlo simulation, the computer takes values from these PDFs to calculate risk values for individuals in a simulated population. The distribution of these risk values is provided in the output of the simulation, as shown in the figure.

entered. For example, the concentration of chemical X for which a risk estimate is desired is assumed to be 100, but could be as low as 50 or as high as 200. In this case, the chemical concentration could be entered as a distribution of values, with 100 as the most likely estimate, but with a range extending from 50 to 200. As with variability, the uncertainty associated with various inputs can be combined to produce a PDF showing boundaries of uncertainty associated with a risk estimate. An additional benefit of this approach is that a sensitivity analysis can be used to rank the various sources of uncertainty in terms of their relative contribution to overall uncertainty. If the uncertainty is unacceptably large, a sensitivity analysis can be used to identify the best areas for further analysis or research to reduce uncertainty.

It is possible for a probabilistic risk assessment to address both variability and uncertainty simultaneously. This requires the development of PDFs for both uncertainty and variability. For example, a PDF might be used to portray variability in body weight in the exposed population, and a separate PDF would be used to deal with any uncertainty that the body weight distribution selected accurately reflects the actual body weight distribution of the population in question. (*Note:* This is not an unreasonable uncertainty, since risk assessors almost never have the time and resources to actually weigh everyone in an exposed population and therefore must rely on published body weight data for the general population to create their body weight PDF.) The variability and uncertainty PDFs are then analyzed separately to generate a risk distribution with confidence boundaries provided by the uncertainty distributions. This is called a *two-dimensional probabilistic risk assessment.*

The principal advantage of a probabilistic risk assessment is that it provides much greater information on variability and uncertainty associated with risk estimates. The manner

in which risk is distributed within the exposed population is transparent, and the magnitude of uncertainty associated with the risk estimate is conveyed in quantitative terms. There are, however, a number of disadvantages to probabilistic risk assessment, including the following: (i) it is technically demanding, requiring much greater expertise than deterministic risk calculations; (ii) it is information intensive, requiring data on exposure characteristics within populations that may not exist; (iii) because of the two previous points, it is much more time consuming and expensive than deterministic risk assessments; (iv) although they provide much more information, the outputs can be complex and difficult for nontechnical audiences to understand; and (v) it requires a different set of policy assumptions regarding acceptable risk. Unlike the situation with a single risk value, acceptable risk must be defined in terms of an acceptable risk distribution.

23.7 EVALUATING RISK FROM CHEMICAL MIXTURES

The simplest form of risk assessment deals with health risks posed by exposure to a single chemical from a single source. Unfortunately, in reality, things are seldom this simple. In most situations, exposure occurs not to a single chemical in high doses (as in toxicology studies in animals), but rather to multiple chemicals in lower doses. Often, more than one of these chemicals is capable of affecting the same target organ or tissue. In this situation, evaluating the risk for individual chemicals one by one may not accurately portray the risk associated with these chemicals in combination. In developing credible risk assessments, it is important not only to consider the cumulative impact of different chemicals affecting the same target organ but also to recognize the potential for these chemicals to interact. Effects of chemicals in combination may not be simply additive. Biological and chemical interactions among the chemicals can lead them to antagonize the effects of one another or produce effects greater than the sum of their individual effects. The ability to account for such interactions and develop meaningful estimates of risks of chemicals in combination is one of the most significant challenges in risk assessment.

There are three basic approaches to evaluating the toxic potential of chemicals in combination. If toxicity data are available for the specific chemical mixture of interest, a preferred approach is to treat the mixture as a single toxicological entity. That is, toxicological data from animals treated with the mixture can be used to identify an RfD, BMD, or slope factor for use in the risk assessment. For this approach to be valid, the chemical mixture to which individuals are exposed must be the same as the mixture used in the toxicity studies, not only in terms of the specific chemicals present but also their proportions. A second approach involves using toxicity data from a "sufficiently similar" mixture, if available, to develop a risk estimate. A similar mixture might, for example, have the same constituents but slightly different proportions, it might have several common components but lack one or two, or it might have one or more additional components. Similar mixtures would be expected to act by the same mechanism of action or produce the same type of toxicity. Beyond these general expectations, there are no firm criteria as to what constitutes "sufficiently similar," leaving this decision up to the judgment of the toxicologist or risk assessor.

If inadequate toxicity data are available for an identical or similar mixture, a third approach is to assess the toxicity of the mixture based on toxicity of its components. This last approach invariably requires assumptions regarding the presence and nature of chemical interactions. Interaction in this context means that one chemical alters the toxicity of one or more other chemicals in the mixture. The default assumption is usually no interaction among the chemicals; that is, in the absence of evidence to the contrary, the chemicals are assumed to act independently—each neither enhancing nor reducing the effect of the others. Chemicals that produce the same toxic effects are considered to act in an additive fashion in this situation, and the total risk is the sum of the risks posed by the individual component chemicals.

Although seemingly simple in concept, in practice, there are several ways to add the effects of chemicals. One way is to use *dose addition*, where the chemicals are considered functional clones of each other. This means that they produce the same toxic effects (or at least the same toxic effect of interest) through the same mode of action and have similar pharmacokinetic properties. These chemicals do not necessarily have identical dose–response curves, and in fact, there can be substantial differences in toxic potency. However, the relationships between the dose–response curves are such that differences in potency between chemicals can be represented by some constant proportion (e.g., one chemical might produce the same toxic response as another, but always at 1% of the dose). Experimentally, dose–response curves of such agents are parallel.

For groups of chemicals that fit this description, combined risks can be calculated using the *relative potency factor* (RPF) approach. One chemical in the mixture (usually the best characterized toxicologically) is designed as the *index chemical* and assigned an arbitrary potency factor of 1. Dose–response information for other chemicals is used to assign each a potency factor relative to the index chemical. For example, a chemical with a potency of 1/100th the index chemical would be assigned an RPF of 0.01, while a chemical 10 times as potent as the index chemical would have an RPF of 10. In the risk assessment, these RPF values are used to convert doses of the various chemicals in the group to toxicologically equivalent doses of the index chemical. These doses are then summed and used, along with a toxicity value for

the index chemical (e.g., RfD, slope factor, as appropriate) to derive a risk estimate for the group as a whole.

The RPF values for chemicals in the group may vary depending on the toxic effect of concern and perhaps the exposure circumstances. There are a few examples where all of the toxic effects of concern share a common mode of action and a single scaling factor is applicable for all effects and exposure conditions. This represents a special case of the RPF method termed the *toxic equivalency factor* (TEF) approach. An example of the use of the TEF approach is the risk assessment of polyhalogenated aromatic compounds. Most of the adverse health effects of concern for these compounds are thought to arise from a common mode of toxicity: Ah receptor activation. In this example, the index chemical is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), which is assigned a relative potency of 1. Based on studies of comparative potency in terms of Ah receptor-mediated toxicity, comparative potency factors (termed TEFs) have been determined for other polyhalogenated aromatics (e.g., PCDDs, PCDFs, PCBs). TEFs for PCB congeners relative to 2,3,7,8-TCDD are listed in Table 23.3. In assessing risks from exposure to a mixture of PCB congeners using the TEF approach, the TEF equivalents for all congeners present in the environmental sample are summed to derive a risk estimate for the PCB mixture.

Another means of adding chemical effects is the *HI* approach. This approach does not require the assumption of a common mode of toxicity, only that the chemicals share the same target organ or effect. In this approach, the dose of each chemical is compared with some representation of a threshold dose for toxicity. In practice, that may be an RfD or a BMD (see Section 23.3 for a discussion of reference and BMDs and their derivation). The dose for which a risk estimate is sought is divided by the threshold dose for that chemical in the target organ of interest and the result is termed the *HQ*. For example, if exposure to a chemical is predicted to result in a dose of 1 mg/kg · day, and the safe dose for the toxicity of concern is 10 mg/kg · day, the HQ is 1/10 or 0.1. HQ for each chemical affecting the target organ is then summed to obtain the HI. The interpretation of the magnitude of the HI is similar to that already discussed (see Section 23.3).

TABLE 23.3 Proposed Toxic Equivalency Factors (TEFs) for PCB Congeners Relative to Dioxin

IUPAC No.	Congener	TEF
	2,3,7,8-TCDD	1
77	3,3′,4,4′-TCB	0.0001
81	3,4,4′,5-TCB	0.0003
126	3,3′,4,4′,5-PeCB	0.1
169	3,3′,4,4′,5,5′-HxCB	0.03
105	2,3,3′,4,4′-PeCB	0.00003
114	2,3,4,4′,5-PeCB	0.00003
118	2,3′,4,4′,5-PeCB	0.00003
123	2′,3,4,4′,5-PeCB	0.00003
156	2,3,3′,4,4′,5-HxCB	0.00003
157	2,3,3′,4,4′,5′-HxCB	0.00003
167	2,3′,4,4′,5,5′-HxCB	0.00003
189	2,3,3′,4,4′,5,5′-HpCB	0.00003

Source: Adapted from Van den Berg et al. (2006).

Yet another way in which effects can be added is through *response addition*. This differs from dose addition methods in that the chemicals and their effects are assumed to be completely independent. For this approach, the percent of animals or humans expected to develop toxicity from each of the individual chemicals at their respective doses is estimated. These percentages are termed the "*responses*." The probability that a toxic event will result from a combination of two chemicals can be expressed as follows:

$$R_{\text{both}} = 1 - (1 - R_{\text{chemical A}}) \times (1 - R_{\text{chemical B}})$$

When the probabilities are small, this reduces to simply

$$R_{\text{both}} = R_{\text{chemical A}} + R_{\text{chemical B}}$$

This approach is considered to be useful in summing a series of small component risks, but does not work well when one or more of the risks are large. In practice, response addition is used primarily in developing estimates of total cancer risks from more than one chemical or from chemical exposure by more than one route.

Each of the aforementioned approaches to combining risks assumes no interaction among chemicals. This is not always the case. It is possible that in some instances one chemical might antagonize or inhibit the toxicity of another. In this situation, the combination of chemicals would produce less-than-additive toxicity. This could conceivably occur through a variety of means depending on the mechanism(s) of toxicity of the chemicals and their toxicokinetics. Examples include effects to decrease toxicant absorption, increase its elimination or decrease its bioactivation, competition for receptor binding, or production of an opposing biochemical or physiological effect. Chemicals in combination can also produce greater-than-additive effects. When both chemicals are capable of producing the effect, this is termed *synergism*. The special case in which one of the two chemicals has no effect on its own, but nonetheless increases the toxicity of another, is termed *potentiation*.

There are a number of tests available to determine whether two chemicals interact in an additive, subadditive (i.e., antagonistic), or supra-additive (i.e., synergistic) fashion. One of the most straightforward is the construction of an isobologram (see Figure 23.8). A straight line is constructed on the graph representing dose pairs that would produce a specified effect level if there were no interaction between the chemicals. This line, an additivity line, varies in slope according to the relative potencies of each chemical. If the

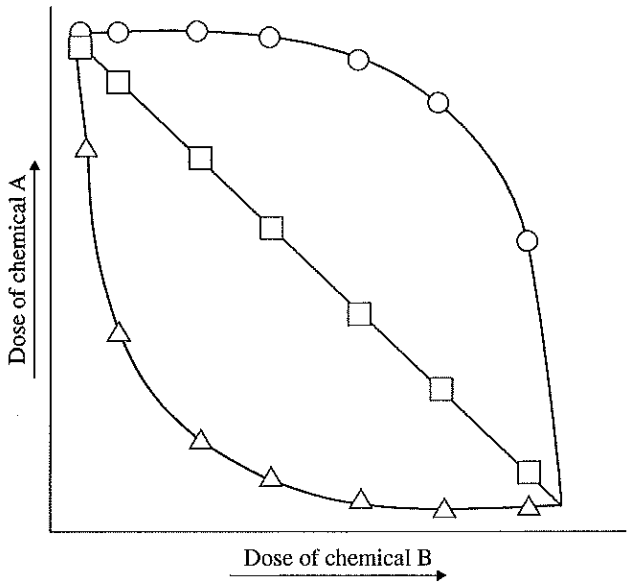

FIGURE 23.8 Isobologram of effects of two chemicals administered in varying dose combinations. The response obtained from chemical A is on the y-axis, and the response from chemical B is plotted on the x-axis. When there is no interaction between the chemicals, the responses from doses comprised of varying proportions of chemicals A and B will fall on the straight line (squares in the figure). If there is synergism between the chemicals, responses to combinations of the chemicals will lie below and to the left of this line (triangles), and antagonistic responses will lie above and to the right of the line (circles).

interaction between the two chemicals follows dose addition, their responses will lie along the additivity line. If the responses to chemical combinations are greater than would be predicted by dose addition, that is, if they lie below and to the left of the dose addition line, a synergistic effect can be inferred. This is because, in the presence of chemical A, a smaller dose of chemical B is needed to achieve the same effect. On the other hand, responses above the line and to the right indicate antagonism.

From a practical standpoint, interactions among chemicals are very difficult to deal with quantitatively in a risk assessment. These interactions are seldom well characterized and can be dose dependent such that synergism or antagonism that occurs at one dose combination of the chemicals may not occur at other dose combinations. Also, while tests exist to examine the nature of interactions between two chemicals, as described in the paragraph earlier, interactions among multiple chemicals are much more difficult to assess and characterize. Although the problem of addressing chemical interactions has been recognized for some time, research to solve this problem is still in a relatively early stage of development. Scientists are still struggling to identify circumstances where important interactions might take place, and rigorous techniques for adjusting risk estimates to account for interactions do not yet exist.

23.8 COMPARATIVE RISK ANALYSIS

For the purposes of this chapter, comparative risk analysis is a means of placing estimates of risk into a larger context in order to provide risk managers and stakeholders with a better perspective for decision making. Comparative risk analysis can also help nontechnical audiences understand the implications of a risk assessment, particularly when findings are reported in unfamiliar quantitative jargon. Furthermore, risk comparisons may be of value in setting priorities and allocating resources within regulatory agencies. In response to many risk problems posed by chemical exposure, the following questions might be asked, all of which would prompt a comparative risk analysis: (i) whether the receptors are exposed to the same chemical from other sources, (ii) whether exposure to the chemical also occurs from other environmental media, and (iii) whether other chemicals from the same sources pose additional risks to receptors. Several types of risk comparisons are listed below.

1. Comparisons of magnitude such as equating a "one-in-one-million" risk to the length of 1 inch in 16 miles, 30 s in a year, or 1 drop in 16 gallons
2. Comparisons of risk posed by the same chemical from different sources
3. Comparisons of risk posed by different chemicals from the same source
4. Comparisons of risk posed by different chemicals for the same target organ
5. Comparisons of familiar versus less familiar risks
6. Comparisons of voluntary versus involuntary risks
7. Comparisons of natural versus anthropogenic or technologic risks
8. Comparisons of risks of the same magnitude posed by different risk factors

Just as risk comparisons can be of value, they can also hinder risk communication. For example, inappropriate comparisons can be confusing and may serve to minimize risks that, in reality, deserve serious consideration. To maximize the benefits of risk comparison and avoid its pitfalls, it is recommended that substantially dissimilar risks (e.g., risk of cancer versus risk of losing money in the stock market) not be compared since the relative magnitudes of such risks are difficult to comprehend. Also, research on risk perception has suggested that directly comparing voluntary and involuntary risks or natural and technologic risks does not always improve a layperson's understanding of an environmental risk. However, the risk comparisons described in list items 2, 3, and 4 above are thought to be of communicative value.

There are no shortages of data available for risk comparisons, since we all incur risks by virtue of our continuous exposure to chemicals at work and at home. Indeed, the

TABLE 23.4 Cancer Risks for Indoor Air Exposures to VOCs

Chemical	Indoor Exposure Levels ($\mu g/m^3$)[a]	Potency $(\mu g/m^3)^{-1} \times 10^{-6}$	Lifetime Cancer Risk ($\times 10^{-6}$)
Benzene	15	3.3	50
Ethylbenzene	13	0.5	6
Methylene chloride	510	0.2	98
Tetrachloroethylene	7	1.2	8.6
Trichloroethylene	2.1	45	95
Chloroform	6.2	9.0	56
Vinyl chloride	0.04	2.5	0.1
Carbon tetrachloride	0.94	6.3	5.9

Source: Adapted from U.S. EPA (2011).
[a]Based on the maximum reported 90th percentile concentration measured in North American residences between 1990 and 2005.

TABLE 23.5 Cancer Risks for Household Exposures to Pesticides in the Lower Rio Grande Valley of Texas

Pesticide	Exposure (ng/m^3)[a]	Potency $(mg/kg \cdot day)^{-1}$	Lifetime Cancer Risk ($\times 10^{-6}$)
Heptachlor	1.6	525	840
Chlordane	1.8	42	75
Dieldrin	1.0	1890	1890
DDD	0.4	40	16
DDE	1.0	40	40
DDT	1.8	40	72
g-BHC (lindane)	11.6	150	1760
Simazine	0.4	14	5.6
Atrazine	3.2	27	86

Source: Adapted from Mukerjee et al. (1997).
[a]Based on the indoor median concentration detected in the spring.

TABLE 23.6 The Therapeutic and Virtually Safe Dosages (VSD) of a Few Medications

Drug	Cancer Slope Factor $(mg/kg \cdot day)^{-1}$	VSD ($mg/kg \cdot day$)	Dose Ratio (Daily Dose/VSD)	ILCR[a] per Daily Dose of Drug (10^{-6})[b]
Rifampin	2.1	4.8×10^{-7}	18,000,000	704.5
Isoniazid	4.9×10^{-1}	2.1×10^{-6}	2,400,000	93.9
Clofibrate	5.4×10^{-2}	1.9×10^{-5}	1,500,000	58.7
Disulfiram	3.6×10^{-1}	2.8×10^{-6}	1,300,000	50.9
Phenobarbital	2.9×10^{-1}	3.5×10^{-6}	825,000	32.3
Acetaminophen	1.3×10^{-2}	7.6×10^{-5}	747,000	29.2
Metronidazole	4.4×10^{-2}	2.3×10^{-5}	467,000	18.3
Sulfisoxazole	1.9×10^{-3}	5.3×10^{-4}	215,000	8.4
Dapsone	1.7×10^{-1}	5.8×10^{-6}	123,000	4.8
Methimazole	4.8×10^{-1}	2.1×10^{-6}	102,000	4.0
Oxazepam	1.0×10^{-1}	9.8×10^{-6}	87,700	3.4
Furosemide	6.0×10^{-2}	1.7×10^{-5}	68,723	2.7

Source: Adapted from Waddell (1996).
[a]ILCR—Incremental Lifetime Cancer Risk.
[b]Calculated by dividing Waddell's dose ration by the 25,550 days in a 70-year lifetime to get the incremental lifetime risk per daily dose of drug above the 10^{-6} risk representing the VSD.

potentially hazardous chemicals in the food we eat, the water we drink, and the air we breathe are numerous, and the list continues to grow as new studies are published. In addition, some medications carry a risk of cancer, and because the dosages of these chemicals are high relative to those chemicals found in the environment, over-the-counter medications and prescription drugs may carry significant theoretical risks even when used as intended. The following tables of risk comparisons have been provided to illustrate some different types of risk comparisons that can be made. Tables 23.4 and 23.5 illustrate the risks projected for volatile organic chemicals and pesticides measured in homes during the U.S. EPA study of residential environments (a type 3 risk comparison). Table 23.6 illustrates the theoretical risks associated with taking a daily dose of 12 different drugs (again, a type 3 risk comparison). Table 23.7 shows risk in a slightly different manner. In this table, risks for various activities, diseases, or lifestyle choices are compared by the number of days each is believed to decreases one's life expectancy (a comparison mixing categories 5, 6, and 7).

23.9 RISK COMMUNICATION

In order to be useful, risk assessment results must be effectively communicated to nontechnical audiences. This can include risk managers, legislators, the public, industry, and environmental groups. If risk managers do not understand the results, it can lead to bad regulatory and policy decisions. Public understanding of risk assessment results is also essential if they are to participate in and accept the results of risk-based decision making.

TABLE 23.7 Estimated Average Loss of Life Expectancy from Various Risks, Activities, and Diseases

	Days Lost
Alcohol addiction	4380
Poverty	3285
Smoking cigarettes and being male	2409
Heart disease	1606
Smoking cigarettes and being female	1424
Cancer	1247
Being an unmarried male	1168
Smoking cigars	1168
Being 35% overweight	964
Having less than an eighth-grade education	949
Being an unmarried female	694
Smoking a pipe	511
Stroke and being male	390
Being 25% overweight	303
Driving motor vehicle	207
Being a mine/quarry worker	167
Suicide	115
Pneumonia, influenza	105
Homicide	93
Misusing legal drugs	92
Diabetes	82
Accidents in the home	74
Falls	28
Suffocation	28
Oral contraceptives	25
Drowning	24
Generation of energy	24
Employment that entails radiation exposure	23
Fires and burns	20
Solid and liquid poisons	20
Dog bites	15
Natural radiation	10
Medical X-ray exposure	10
Firearm accidents	6.5
Riding a bicycle	6
Poisonous gases	4
Bee stings	0.2
Radiation from the nuclear industry	0.06

Source: Adapted from Cohen (1991, 2003).

Effectively communicating the results of risk assessments is an enormous challenge. Problems lie in virtually all aspects of the risk communication process, including (i) the individual, agency, or company that conducts and presents the risk assessment, (ii) the risk assessment itself, (iii) the means to convey risk information, and (iv) the audience. Examples of these problems are listed in Table 23.8. One of the biggest hurdles is the fact that risk analyses are often very complex, technical exercises. Making the process and outcome of the risk analysis transparent to laypersons is next to impossible unless there is some opportunity to provide background education to "bring them up to speed" on the subject. In most situations, this opportunity does not exist. The public is arguably one of the most important recipients of risk information yet one of the most difficult audiences for risk assessors to communicate with. One problem is that the most common channel for communicating risk information to the public is through the news media. This presents at least three difficulties in trying to communicate a clear and accurate message: (i) reporting of the information may be biased, incomplete, or inaccurate; (ii) news accounts may tend to sensationalize or focus on ancillary issues, such as disagreements between parties or human interest stories; and (iii) news media have generally shown little interest in providing the background information needed to educate the public on risk analysis and to help them interpret findings for themselves.

No doubt one reason why the media have not invested much effort in educating the public about risk assessment is that the public itself, for the most part, has shown little interest in the technical complexities and nuances of risk analysis. In most situations for which a risk assessment is needed, they just want a straight answer to the simple questions, "Is it safe?" Anything other than a clear "yes" answer to this question signals cause for concern. Herein lies a second major problem for risk communication. Unfortunately, all too often, the answers conveyed by the risk assessment can seem ambiguous. Scientists are trained to be circumspect in their conclusions and carefully point out any caveats in their analysis. This certainly applies to risk assessments, where responsible presentation of risk estimates is always accompanied by a discussion of the many areas of uncertainty and limitations in the analysis. When all of the caveats and uncertainties are presented along with the risk estimate, the uncertainty looms large and it is easy for the public to conclude "they don't really know what the risk is." When this happens, regardless of whether the risk estimates themselves are large or small, they have little credibility. Thus, the dilemma for the risk communicator is how to adequately convey the underlying uncertainties in the risk estimates without losing the essential message that the risks are large or small, as the case may be.

Deciding whether a risk is acceptable requires, in part, placing that risk in context. Thus, the risk from a particular chemical or set of exposure circumstances could be compared with other risks to the individual or population in order to place that risk in perspective. While this is straightforward in concept, it is difficult in practice, particularly when communicating risk to the general public. One reason is that the public, unaccustomed to seeing typical risk assessment outputs, may have little basis for comparison. Unless someone has experience with, or is shown, comparative risk data for a variety of hazards, it is difficult for them to know whether a 1×10^{-5} risk is significant. For noncancer health effects, the meaning of outputs in terms of HI or margin of exposure is even more obscure. How, for example, would you help citizens place an HI of 3 for a chemical exposure in the context of risk from events in their everyday lives?

TABLE 23.8 Examples of Risk Communication Problems

Source of Problem	Examples
Source of the message	The source of the risk information is not usually trained in communication skills
	The source of the risk information, usually a governmental or industrial entity or representative, is not trusted due to a history of exaggeration, secrecy, or worse
	Any disagreements among scientific experts make the information appear to be guesswork
	The risk assessment may not have received stakeholder input and, therefore, not address issues of greatest concern to individuals and communities
The message	Risk estimates may have large uncertainties due to limitations in data used in the risk assessment
	Risk assessments do not provide exact answers about the actual nature of the risk
Channel for conveying the message	Media interpretation may result in presentation of oversimplified, distorted, or erroneous information
	Media emphasis on drama, wrongdoing, or conflicts clouds presentation of risk information
	Journalists do not often have the scientific background needed to evaluate the disagreements or debates surrounding the risk estimates
Receiver of the message	Public perceptions of risk are often inaccurate
	There may be unrealistic demands for scientific certainty in risk estimates
	There may be a lack of interest in learning the technical complexities of the risk assessment and therefore a poor understanding of what risk estimates represent
	There may be difficulty in understanding risk if it relates to unfamiliar activities or technologies or is presented in an unfamiliar way
	Not everyone will be open minded; some individuals with strong opinions and beliefs will not be receptive to information that contradicts them
	Risks are usually perceived more in terms of outrange (or lack thereof) than actual harm or hazard

Source: Adapted from Covello and Sandman (2001).

A second reason that placing risks in context for the public is difficult is that the public often has distorted views of the risks posed by common and uncommon events in their lives. Comparing risks from chemical exposure to risks the public is more familiar is valuable only if their point of reference is accurate, and unfortunately, it seldom is. This has been demonstrated repeatedly in studies in which survey respondents' estimates of risks or comparative risk rankings for various hazards were compared with the actual, measured risks. Presenting the public with accurate risk comparisons can be helpful, but does not necessarily solve the problem. There are at least two reasons for this. One is that the meaning of the term "risk" itself is often different for the risk assessor and the public. The risk assessor tends to define risk as a probability of an adverse health effect and thinks of risk in purely probability terms. It is not surprising, then, that risk assessors once thought that a comparison of probabilities is all the public needs to place risks in perspective. The public, however, does not view risk simply in probability terms. The perception of the risk can be shaped powerfully by the nature of the risk (e.g., what health effect is at risk, such as cancer), whether the risk is voluntary or involuntary and whether the risk is accompanied by any perceived benefits.

Several strategies have evolved for improving risk communication. The first is to pay very careful attention to the language that is used in risk communication. Of course, jargon and acronyms unfamiliar to the public should be avoided. It is also important to understand that terms and expressions in common use in risk assessment have very different meanings to the public. For example, a "conservative approach" is understood in risk assessment to mean one protective of health, while the public might mistakenly interpret this as a risk assessment approach endorsed by one end of the political spectrum (e.g., as opposed to a "liberal approach"). In order to be more protective, an agency might "lower the standards" for a chemical, meaning to decrease permissible concentrations. To the public, however, lowering standards might be misinterpreted as allowing some sort of deterioration in their protectiveness. To avoid awkward and sometimes disastrous misunderstandings, it is important to carefully scrutinize the risk communication message and remove terms and phrases that will be unclear or have a different meaning for the public.

It is an unfortunate fact that there are few sources that the public explicitly trusts for risk information. Risk information provided by industry is often met with skepticism. In particular, risk messages that indicate no harm or basis for concern for chemical exposure are seen as self-serving. Credibility of governmental agencies charged with protecting public health and the environment is better, but not much. In dealing with the public, particularly when engaging them directly (e.g., through public meetings), it is extremely

important to be open and honest. An individual seen as not forthcoming with information, or who provides information solely as "technical gibberish," will be regarded as either completely out of touch or hiding something. From a risk communication standpoint, one is just as bad as the other. It is also important to listen to the public and gain an appreciation for their concerns and fears. Engaging in dialog early in the risk assessment process has several benefits, including the following:

1. It helps ensure that the risk assessment will be able to answer questions of greatest interest to the public.
2. Individuals in the public may be able to offer knowledge useful to the risk assessment, such as historical perspective and information regarding the manner in which individuals are (or have been) exposed to the chemicals in question.
3. It affords the opportunity to establish trust with the public. Of course, demeanor is important; a condescending manner is a sure way to cut the lines of risk communication.

23.10 SUMMARY

Conceptually, the basic components of any risk assessment are (i) hazard identification (what health effects may be produced by specific chemicals), (ii) dose–response assessment (what dose of chemical is required to produce these effects), (iii) exposure assessment (whether persons are actually exposed to chemicals and what doses they receive), and (iv) risk characterization (how likely is it that adverse effects will occur, and what are the potential limitations of the risk assessment as performed).

In order to fulfill their goal of ensuring protection of public health, regulatory agencies usually choose conservative exposure and modeling assumptions, namely, those that tend to overestimate rather than underestimate risk. Because the impact of each conservative assumption is frequently multiplicative and cumulative, the final risk estimate may overstate the true population risk substantially. Nonetheless, it is difficult to deviate from this approach given that considerable uncertainty exists for many components of the risk assessment.

While risk assessment has traditionally focused on human health, ecological risk assessments, which address potential impacts to plants and wildlife, are also commonly performed. Ecological risk assessments differ from human health risk assessments in that they are inherently more complex—there are many more species to consider, including interspecies relationships and more complicated exposure modeling—and they tend to focus more on population-, species-, and ecosystem-level effects.

Traditionally, cancer risks have been expressed in probability terms using linear, nonthreshold dose–response relationships. These relationships assume that any dose of a carcinogen poses some risk of developing cancer. The potential for noncancer health effects is evaluated using threshold models, where a dose below which no health effects will occur is assumed to exist. There has been increasing recognition that the dose–response relationship for some carcinogens may also involve a threshold, and methods to take this threshold into consideration in evaluating cancer risk from these chemicals have been used.

Deterministic risk assessments develop a single estimate of risk for a population, usually derived in such a way as to represent an upper-bound estimate. Probabilistic risk assessments can provide a description of the variability of risks within the population and quantitative estimates of uncertainty associated with those risks. While probabilistic risk assessments potentially offer more risk information, deterministic risk assessments are easier to perform and less expensive, and there exists a greater consensus as to how risk outputs should be conveyed and interpreted. At present, deterministic risk assessments are more routinely used because of their simplicity and ease of application.

The risk assessment should be performed in a *transparent* manner; that is, the steps performed should be easy to identify, understand, and evaluate. Also, the outcome of the risk assessment must be communicated in a way that can be understood by those without technical backgrounds, including the public. This is very challenging because risk assessors and the public may view risks and risk issues very differently.

A criticism of risk assessments that produce a numerical estimate of risk (quantitative risk assessments) is that they often convey the impression of greater precision than actually exists. It is vitally important that risk assessments include qualitative information as well, such as a discussion of the uncertainties associated with the risk estimate and the extent to which evidence of a true human hazard is weak or controversial.

It must be recognized that risk assessment is just one aspect of the larger process of risk management. In the development of strategies and procedures to address health concerns for chemical exposures, risk estimates undoubtedly play an important role. However, they are often not the sole consideration. Economic, social, and political factors, as well as technical feasibility, may also influence the management of chemical exposures in modern society.

SUGGESTED READING

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