CHAPTER

4

Risk Assessment

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KEY POINTS

- Risk assessment is the systematic scientific characterization of potential adverse health effects resulting from human exposures to hazardous agents or situations.
- Risk is defined as the probability of an adverse outcome under specified conditions.
- Risk management refers to the process by which policy actions are chosen to control hazards.

INTRODUCTION AND HISTORICAL CONTEXT

Toxicologic research and toxicity testing conducted and interpreted by toxicologists constitute the scientific core of an important activity known as risk assessment for chemical exposures. In 1983, the National Research Council detailed the steps of hazard identification, dose–response assessment, exposure analysis, and characterization of risks in Risk Assessment in the Federal Government: Managing the Process (widely known as The Red Book). The scheme shown in Figure 4–1 provides a consistent framework for risk assessment across agencies with bidirectional arrows showing an ideal situation where mechanistic research feeds directly into risk assessments and critical data uncertainty drives research. Often, public policy objectives require extrapolations that go far beyond the observation of

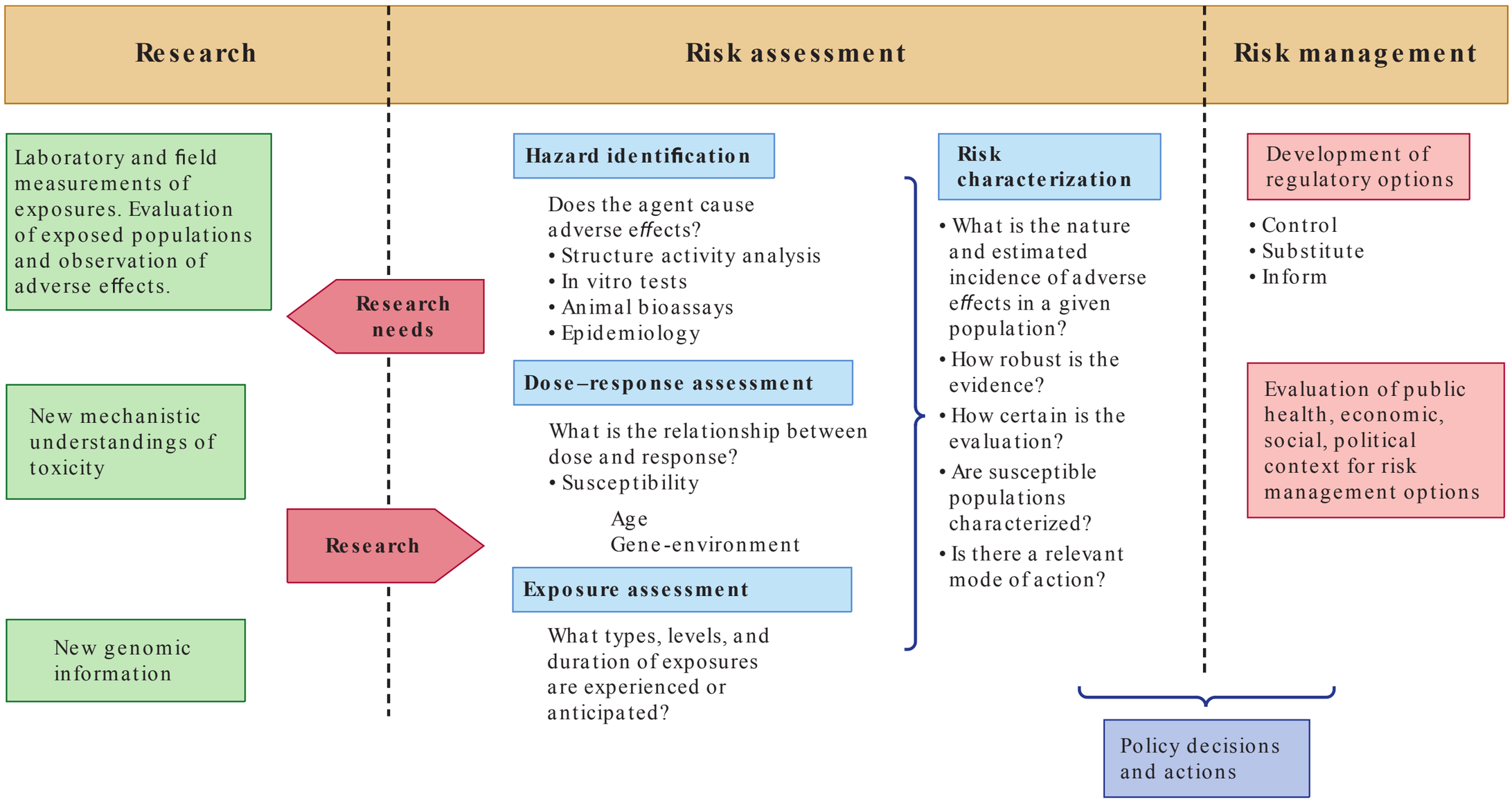

FIGURE 4–1 **Risk assessment/risk management framework.** This framework shows in blue the four key steps of risk assessment: hazard identification, dose–response assessment, exposure assessment, and risk characterization. It shows an interactive, two-way process where research needs from the risk assessment process drive new research, and new research findings modify risk assessment outcomes. (Adapted with permission from Risk Assessment in the Federal Government: Managing the Process, Washington, DC: National Academies Press; 1983.)

actual effects and reflect different tolerances for risks, generating controversy.

A comprehensive framework that applies two crucial concepts: (1) putting each environmental problem or issue into public health and/or ecological context and (2) proactively engaging the relevant stakeholders, affected or potentially affected community groups, from the very beginning of the six-stage process shown in Figure 4–2. Particular exposures and potential health effects must be evaluated across sources and exposure pathways and in light of multiple end points, and not the current general approach of evaluating one chemical in one environmental medium (air, water, soil, food, and products) for one health effect at a time.

DEFINITIONS

Risk assessment is the systematic scientific evaluation of potential adverse health effects resulting from human exposures to hazardous agents or situations. Risk is defined as the probability of an adverse outcome based on the exposure and potency of the hazardous agent(s). The term hazard refers to intrinsic toxic properties, whereas exposure becomes an essential consideration along with hazard for risk determination. Risk assessment requires qualitative information about the strength of the evidence and the nature of the outcomes—as well as quantitative assessment of the exposures, host susceptibility factors, and potential magnitude of the hazard—and then a description of the uncertainties in the estimates and conclusions. The objectives of risk assessment are outlined in Table 4–1.

The phrase characterization *of* risk reflects the combination of qualitative and quantitative analyses. Unfortunately, many users tend to equate risk assessment with quantitative risk assessment, generating a number for an overly precise risk estimate, while ignoring crucial information about the uncertainties of risk assessment, mode of action (MOA), and type of effect across species or context.

Risk management refers to the process by which policy actions are chosen to control hazards identified in the risk assessment/risk characterization stage of the framework (Figure 4–2). Risk managers consider scientific evidence and risk estimates—along with statutory, engineering, economic, social, and political factors—in evaluating alternative options and choosing among those options.

Risk communication is the challenging process of making risk assessment and risk management information comprehensible to community groups, lawyers, local elected officials, judges, business people, labor, environmentalists, etc. A crucial, too-often neglected requirement for communication is listening to the fears, perceptions, priorities, and proposed remedies of these "stakeholders."

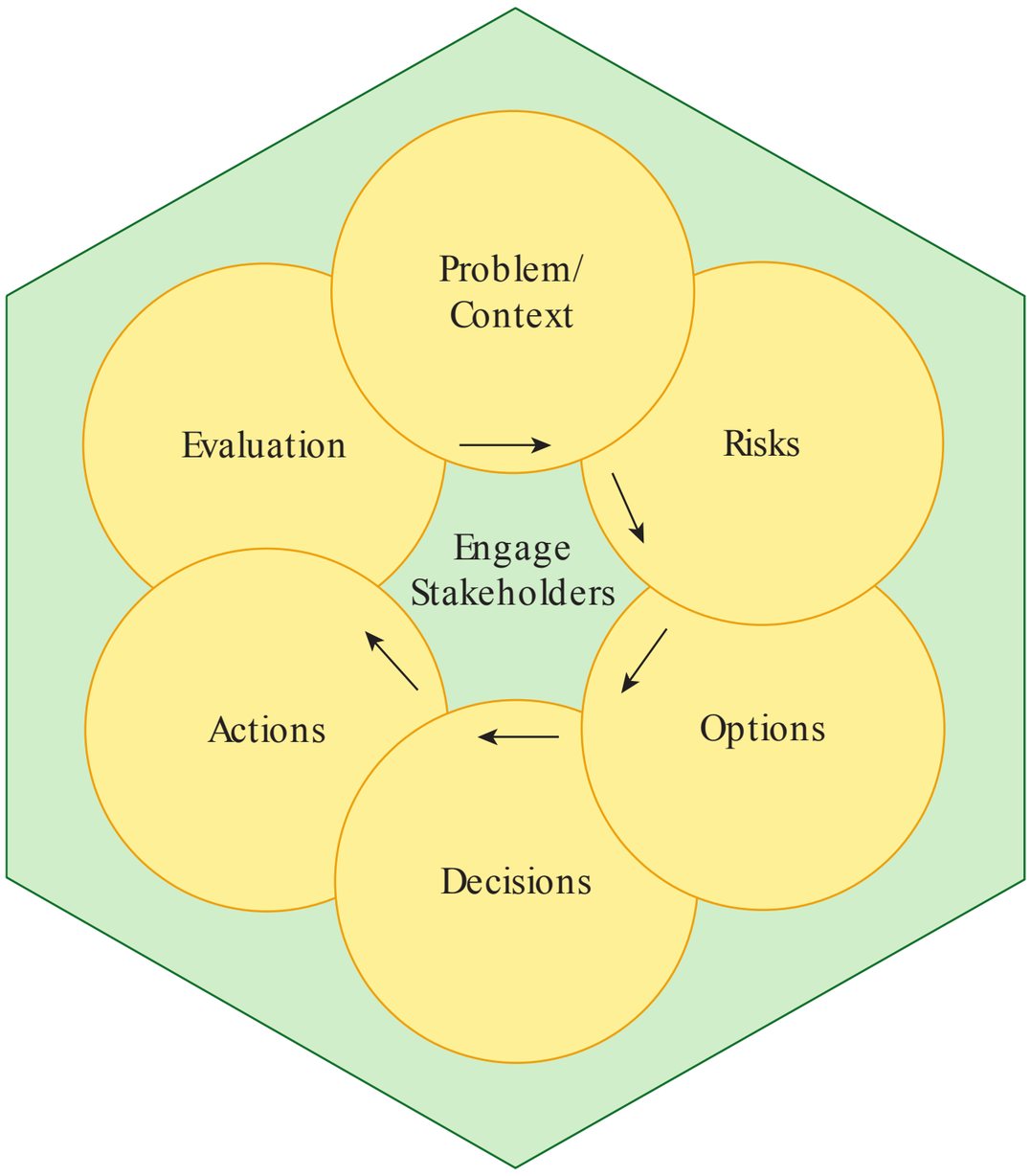

FIGURE 4–2 **Risk management framework for environmental health from the U.S. Commission on Risk Assessment and Risk Management.** The framework comprises six stages: (1) formulating the problem in a broad public health context, (2) analyzing risks, (3) defining options, (4) making risk-reduction decisions, (5) implementing those actions, and (6) evaluating the effectiveness of the taken actions. Interactions with stakeholders are critical and thus have been put at the center of the framework.

DECISION MAKING

Risk management decisions are reached under diverse statutes in the United States and many other countries. Some statutes specify reliance on risk alone, whereas others require a balancing of risks and benefits of the product or activity (Table 4–1). Risk assessments provide a valuable framework for priority setting within regulatory and health agencies, in the chemical development process within companies, and in resource allocation by environmental organizations. Currently, there are significant efforts toward a global harmonization of testing protocols and the assessment of risks and standards.

A major challenge for risk assessment, risk communication, and risk management is to work across disciplines to demonstrate the biological plausibility and clinical significance of the conclusions from studies of chemicals thought to have potential adverse effects. Biomarkers of exposure, effect, or individual susceptibility can link the presence of a chemical in various environmental compartments to specific sites of action in target organs and to host responses. Individual behavioral and social risk factors may be critically important to both the characterization of risk and the reduction of risk. Finally, public and media attitudes toward local polluters, other responsible parties, and relevant government agencies can greatly influence the communication process and the choices for risk management.

TABLE 4–1 Objectives of risk assessment.

1. Protect human and ecological health Toxic substances
2. Balance risks and benefits Drugs Pesticides
3. Set target levels of risk Food contaminants Water pollutants
4. Set priorities for program activities Regulatory agencies Manufacturers Environmental/consumer organizations
5. Estimate residual risks and extent of risk reduction after steps are taken to reduce risks

HAZARD IDENTIFICATION

Assessing Toxicity of Chemicals—Introduction

In order to assess toxicity of chemicals, information from four types of studies is used: structure–activity relationships (SAR), in vitro or short-term studies, in vivo animal bioassays, and information from human epidemiologic studies. In many cases, toxicity information for chemicals is limited; however, recent efforts to mitigate this gap in understanding have been successful.

Assessing Toxicity of Chemicals—Methods

Structure/Activity Relationships (SARs)—Given the cost of $2 to $4 million and the 3 to 5 years required for testing a single chemical in a lifetime rodent carcinogenicity bioassay, initial decisions on whether to continue development of a chemical, submit a premanufacturing notice, or require additional testing may be based largely on SARs and limited short-term assays. A chemical's structure, solubility, stability, pH sensitivity, electrophilicity, volatility, and chemical reactivity can be important information for hazard identification.

SARs have been used for assessment of complex mixtures of structurally related compounds. However, it is difficult to predict activity across chemical classes and especially across multiple toxic end points using a single biological response. Pharmaceutical companies are now using computerized combinatorial chemistry and three-dimensional (3D) molecular modeling approaches to design new drugs (ligands) that can sterically fit into the "receptors of interest." However, computerized SAR methods have given disappointing results because it is rare for environmental pollutants to exhibit selective ligand–receptor binding.

In Vitro and Short-term Tests—The next approach for hazard identification comprises using tests ranging from in vitro bacterial mutation assays to more elaborate short-term tests such as skin-painting studies in mice or altered rat liver foci assays conducted in vivo, as well as other assays that evaluate developmental, reproductive, neuro-, and immunotoxicity.

Short-term assay validation and application is particularly important to risk assessment because such assays can provide information about mechanisms of effects while being faster and less expensive than lifetime bioassays. Validation requires determination of their sensitivity (ability to identify true carcinogens), specificity (ability to recognize noncarcinogens as noncarcinogens), and predictive value for the toxic end point under evaluation. Considerable effort to improve the utility of these tests is continually expended due to their value in providing chemical-specific mechanistic information.

Animal Bioassays—Animal bioassay data are key components of the hazard identification process. A basic premise of risk assessment is that chemicals that cause tumors in animals can cause tumors in humans. All human carcinogens that have been adequately tested in animals produce positive results in at least one animal model. Although this association cannot establish that all agents and mixtures that cause cancer in experimental animals also cause cancer in humans, nevertheless, in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans—a reflection of the "precautionary principle." In general, the most appropriate rodent bioassays are those that test exposure pathways of most relevance to predicted or known human exposure pathways. Bioassays for reproductive and developmental toxicity and other noncancer end points have a similar rationale.

Consistent features in the design of standard cancer bioassays include testing in two species and both sexes, with 50 animals per dose group and near-lifetime exposure. Important choices include the strains of rats and mice, the number of doses, and dose levels (typically 90%, 50%, and 10% to 25% of the maximally tolerated dose [MTD]), and the details of the required histopathology (number of organs to be examined, choice of interim sacrifice pathology, etc.). Positive evidence of chemical carcinogenicity can include increases in number of tumors at a particular organ site, induction of rare tumors, earlier induction (shorter latency) of commonly observed tumors, and/or increases in the total number of observed tumors.

Critical problems exist in using the hazard identification data from rodent bioassays for quantitative risk assessments. This is because of the limited dose–response data available from these rodent bioassays and nonexistent response information for environmentally relevant exposures. Results thus have traditionally been extrapolated from a dose–response curve in the 10% to 100% biologically observable tumor response range down to 10^{-6} risk estimates (upper confidence limit) or to a benchmark or reference dose-related risk.

Lifetime bioassays have been enhanced with the collection of additional mechanistic data and with the assessment of multiple noncancer end points. It is feasible and desirable to integrate such information together with data from mechanistically oriented short-term tests and biomarker and genetic studies in epidemiology. Such approaches may allow for an extension of biologically observable phenomena to doses lower than those leading to frank tumor development and help to address the issues of extrapolation over multiple orders of magnitude to predict response at environmentally relevant doses.

In an attempt to improve the prediction of cancer risk to humans, transgenic mouse models have been developed as possible alternatives to the standard 2-year cancer bioassay. By using mice that incorporate or eliminate a gene that is linked to human cancer, these transgenic models have the power to improve the characterization of key cellular processes and the mode of action of toxicological responses. It is suggested that these models currently should not replace the 2-year assay, but should be used in conjunction with other types of data to assist in the interpretation of additional toxicological and mechanistic evidence.

Use of Epidemiologic Data in Risk Assessment—The most convincing line of evidence for human risk is a well-conducted epidemiologic study in which a positive association between exposure and disease has been observed. Table 4–2 shows examples of epidemiologic study designs and provides clues on types of outcomes and exposures evaluated. There are important inherent limitations in epidemiologic studies. When the study is exploratory, hypotheses are often weak. Exposure estimates are often crude and retrospective, especially for conditions with long latency before clinical manifestations appear. Generally, there are multiple exposures, especially when a lifetime is considered. There is always a trade-off between detailed information on relatively few persons and very limited information on large numbers of persons. Contributions from lifestyle factors, such as smoking and diet, are a challenge to sort out. Humans are highly outbred, so the method must consider variation in susceptibility among those who are exposed.

Nevertheless, human epidemiology studies provide very useful information for hazard identification and sometimes quantitative information for data characterization. Three major types of epidemiology study designs are available: cross-sectional studies, cohort studies, and case–control studies (Table 4–2). Cross-sectional studies survey groups of humans to identify risk factors (exposure) and disease but are not useful for establishing cause and effect. Cohort studies evaluate individuals selected on the basis of their exposure to an agent under study. These prospective studies monitor over time individuals who initially are disease-free to determine the rates at which they develop disease. In case–control studies, subjects are selected on the basis of disease status: disease cases and matched cases of disease-free individuals. Exposure histories of the two groups are compared to determine key consistent features in their exposure histories. All case–control studies are retrospective studies.

TABLE 4–2 Attributes of three types of epidemiologic study designs.

Methodological Attributes	Type of Study		
	Cohort	Case–Control	Cross-sectional
Initial classification	Exposure–nonexposure	Disease–nondisease	Either one
Time sequence	Prospective	Retrospective	Present time
Sample composition	Nondiseased individuals	Cases and controls	Survivors
Comparison	Proportion of exposed with disease	Proportion of cases with exposure	Either one
Rates	Incidence	Fractional (percent)	Prevalence
Risk index	Relative risk–attributable risk	Relative odds	Prevalence
Advantages	Lack of bias in exposure, yields rates of incidence and risk	Inexpensive, small number of subjects, rapid results, suitable for rare diseases, no attrition	Quick results
Disadvantages	Large number of subjects required, long follow-up, attrition, change in time of criteria and methods, costly, inadequate for rare diseases	Incomplete information, biased recall, problem in selecting control and matching, yields only relative risk—cannot establish causation, population of survivors	Cannot establish causation (antecedent consequence), population of survivors, inadequate for rare diseases

Epidemiologic findings are judged by the following criteria: strength of association, consistency of observations (reproducibility in time and space), specificity (uniqueness in quality or quantity of response), appropriateness of temporal relationship (did the exposure precede responses?), dose–responsiveness, biological plausibility and coherence, verification, and analogy (biological extrapolation). In addition, epidemiologic study designs should be evaluated for their power of detection, appropriateness of outcomes, verification of exposure assessments, completeness of assessing confounding factors, and general applicability of the outcomes to other populations at risk. Power of detection is calculated using study size, variability, accepted detection limits for end points under study, and a specified significance level.

Recent advances from the human genome project, increased sophistication of molecular biomarkers, and improved mechanistic bases for epidemiologic hypotheses have allowed epidemiologists to expand our understanding of biological plausibility and clinical relevance. "Molecular epidemiology" with improved molecular biomarkers of exposure, effect, and susceptibility has allowed investigators to more effectively link molecular events in the causative disease pathway. The range of biomarkers has grown dramatically and includes identification of single nucleotide polymorphisms (SNPs), genomic profiling, transcriptome analysis, and proteomic analysis.

Integrating Qualitative Aspects of Risk Assessment

Qualitative assessment of hazard information should include consideration of the consistency and concordance of findings, including a determination of the consistency of the toxicological findings across species and target organs, an evaluation of consistency across duplicate experimental conditions, and a determination of the adequacy of the experiments to consistently detect the adverse end points of interest. Many agencies use similar evidence classification for both animal and human studies. These classifications include levels of sufficient, limited, inadequate, no evidence, or evidence suggesting lack of carcinogenicity. An overall weight of evidence approach to carcinogenicity uses these evidence classifications, and considers the quality and quantity of data as well as any underlying assumptions.

DOSE–RESPONSE ASSESSMENT

Integrating Quantitative Aspects of Risk Assessment

Quantitative considerations in risk assessment include dose–response assessment, exposure assessment, variation in susceptibility, and characterization of uncertainty.

The fundamental basis of the quantitative relationships between exposure to an agent and the incidence of an adverse response is the dose–response assessment. Analysis of dose–response relationships must start with the determination of the critical effects to be quantitatively evaluated. It is usual practice to choose the data sets with adverse effects occurring at the lowest levels of exposure from studies using the most relevant exposure routes. The "critical" adverse effect is defined as the significant adverse biological effect that occurs at the lowest exposure level.

Threshold Approaches—Threshold dose–response relationship characterization includes identification of "no or lowest observed adverse effect levels" (NOAELs or LOAELs). On the dose–response curve illustrated in Figure 4–3, the threshold, indicated as T, represents the dose below which no additional increase in response is observed. The NOAEL is identified as the highest nonstatistically significant dose tested; in this

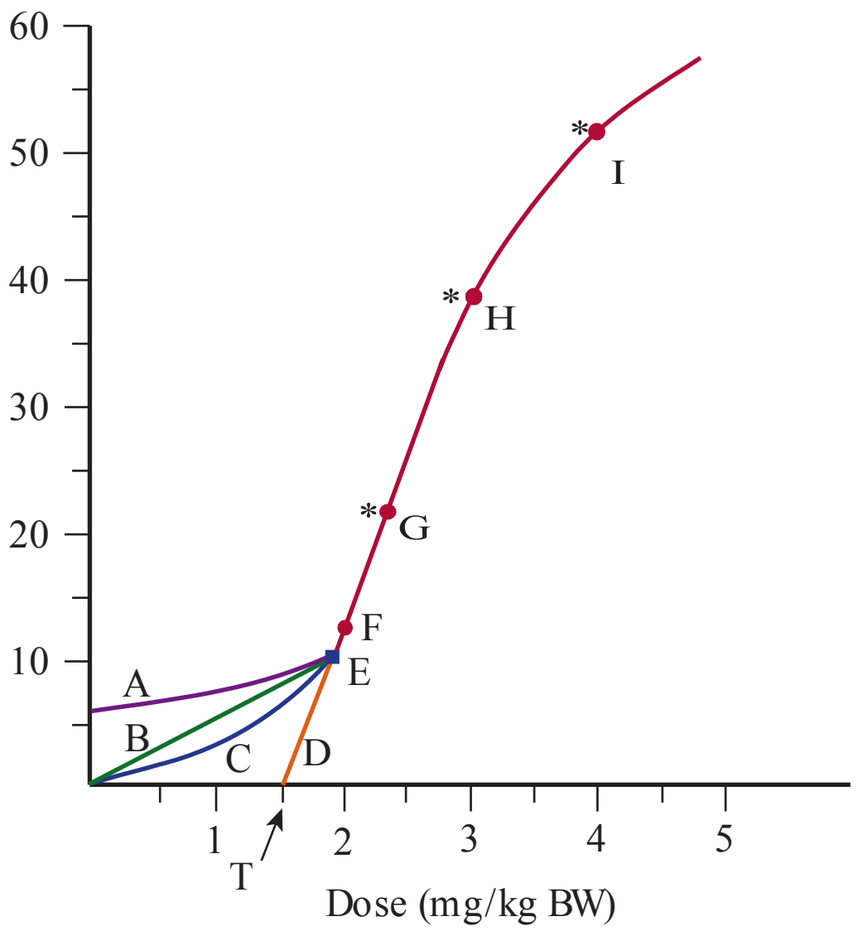

FIGURE 4–3 **Dose–response curve.** This figure is designed to illustrate a typical dose–response curve with points E to I indicating the biologically determined responses. Statistical significance of these responses is indicated with a "*" symbol. The threshold is shown by T, a dose below which no change in biological response occurs. Point E represents the point of departure (POD), the dose near the lower end of the observed dose–response range, below which extrapolation to lower doses is necessary. Point F is the highest nonstatistical significant response point; hence, it is the "no observed adverse effect level" (NOAEL) for this example. Point G is the "lowest observed adverse effect level" (LOAEL) for this example. Curves A to D show some options for extrapolating the dose–response relationship below the range of biologically observed data points and POD.

example it is point F, at 2 mg/kg body weight. Point G is the LOAEL (~2.3 mg/kg body weight), as it is the lowest dose tested with a statistically significant effect. Lines A to D represent possible extrapolations below the point of departure (POD), which is represented on this figure as a square and is labeled as point E. POD is used to specify the estimated dose near the lower end of the observed dose range, below which extrapolation to lower exposures is necessary.

In general, animal bioassays are constructed with sufficient numbers of animals to biological responses at the 10% response range. Significance usually refers to both biological and statistical criteria and is dependent on the number of dose levels tested, the number of animals tested at each dose, and background incidence of the adverse response in the nonexposed control groups. The NOAEL should not be perceived as risk-free.

As described in Chapter 2, approaches for characterizing dose–response relationships include identification of effect levels such as LD_{50} (dose producing 50% lethality), LC_{50} (concentration producing 50% lethality), ED_{10} (dose producing 10% response), as well as NOAELs.

NOAELs have traditionally served as the basis for risk assessment calculations, such as reference doses (RfDs) or acceptable daily intake (ADI) values. RfDs or concentrations (RfCs) are estimates of a daily exposure (oral or inhalation, respectively) to an agent that is assumed to be without adverse health impact in humans. ADI values may be defined as the daily intake of chemical during an entire lifetime, which appears to be without appreciable risk on the basis of all known facts at that time. RfDs and ADI values typically are calculated from NOAEL values by dividing by uncertainty (UF) and/or modifying factors (MF):

$$\text{RfD} = \frac{\text{NOAEL}}{\text{UF} \times \text{MF}}$$

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF} \times \text{MF}}$$

Tolerable daily intakes (TDIs) can be used to describe intakes for chemicals that are not "acceptable" but are "tolerable" as they are below levels thought to cause adverse health effects. These are calculated in a manner similar to ADI. In principle, dividing by these factors allows for interspecies (animal-to-human) and intraspecies (human-to-human) variability with default values of 10 each. An additional UF can be used to account for experimental inadequacies—e.g., to extrapolate from short-exposure-duration studies to a situation more relevant for chronic study or to account for inadequate numbers of animals or other experimental limitations. If only a LOAEL value is available, then an additional 10-fold factor commonly is used to arrive at a value more comparable to a NOAEL. Traditionally, a safety factor of 100 would be used for RfD calculations to extrapolate from a well-conducted animal bioassay (10-fold factor animal-to-human) and to account for human variability in response (10-fold factor human-to-human variability).

MF can be used to adjust the UF if data on mechanisms, pharmacokinetics, or relevance of the animal response to human risk justify such modification.

Recent efforts have focused on using data-derived and chemical-specific adjustment factors to replace the 10-fold UF traditionally used in calculating RfDs and ADIs. Such efforts have included reviewing the human pharmacologic literature from published clinical trials and developing human variability databases for a large range of exposures and clinical conditions. Intra- and interspecies UF have two components: toxicokinetic and toxicodynamic aspects; Figure 4–4 shows these distinctions. This approach provides a structure for incorporating scientific information on specific aspects of the overall toxicologic process into the RfD calculations; thus, relevant data can replace a portion of the overall "uncertainty" surrounding these extrapolations.

NOAEL values have also been utilized for risk assessment by evaluating a "margin of exposure" (MOE), where the ratio of the NOAEL determined in animals and expressed as mg/kg per day is compared with the level to which a human may be exposed. Low values of MOE indicate that the human levels of exposure are close to levels for the NOAEL in animals. Unlike RfD and RfC, there is usually no factor included in this calculation for differences in human or animal susceptibility or animal-to-human extrapolation. Thus, MOE values of less

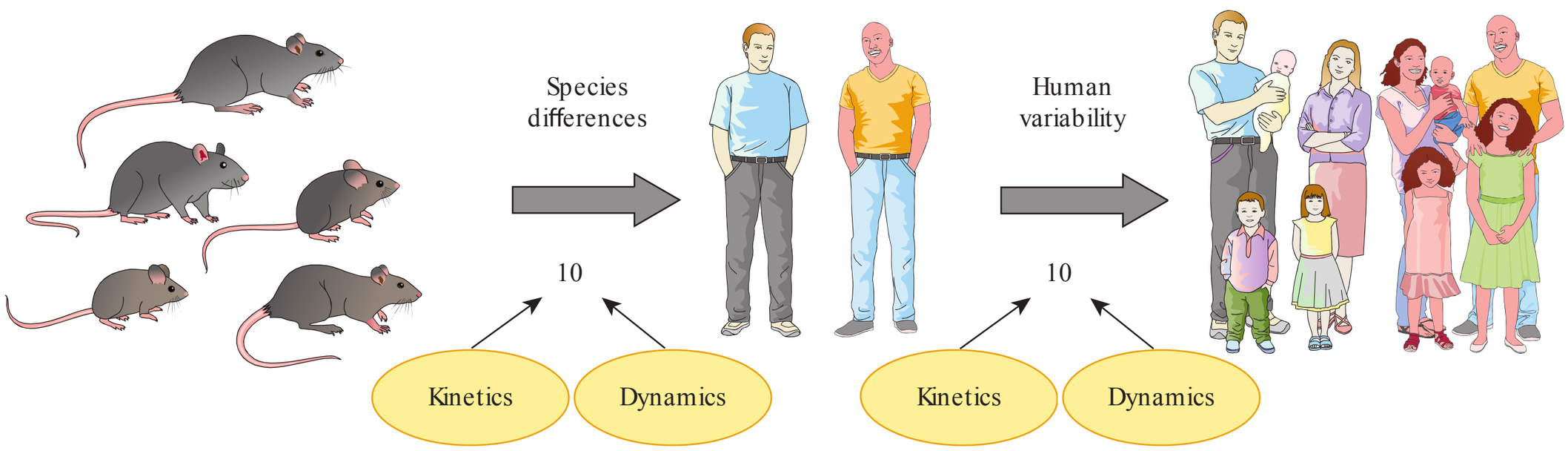

FIGURE 4–4 Toxicokinetic (TK) and toxicodynamic (TD) considerations inherent in interspecies and interindividual extrapolations. Toxicokinetics refers to the processes of absorption, distribution, elimination, and metabolism of a toxicant. Toxicodynamics refers to the actions and interactions of the toxicant within the organism and describes processes at organ, tissue, cellular, and molecular levels. This figure shows how uncertainty in extrapolation both across and within species can be considered as being due to two key factors: a kinetic component and a dynamic component. Refer to the text for detailed explanations.

than 100 have been used by regulatory agencies as flags for requiring further evaluation.

The NOAEL approach has been criticized on several points, including that (1) the NOAEL must, by definition, be one of the experimental doses tested; and (2) once this is identified, the rest of the dose–response curve is ignored. Because of these limitations, an alternative to the NOAEL approach, the benchmark dose (BMD) method, was proposed. In this approach, the dose–response is modeled and the lower confidence bound for a dose at a specified response level (benchmark response [BMR]) is calculated. The BMR is usually specified at 1%, 5%, or 10%. The BMD_x (with x representing the percent BMR) is used as an alternative to the NOAEL value for reference dose calculations. Thus the RfD would be:

$$RfD = \frac{BMD_x}{UF \times MF}$$

The proposed values to be used for the UF and MF for BMDs can range from the same factors as for the NOAEL to lower values due to increased confidence in the response level and increased recognition of experimental variability owing to use of a lower confidence bound on dose.

Advantages of the BMD approach can include (1) the ability to take into account the full dose–response curve; (2) the inclusion of a measure of variability (confidence limit); and (3) the use of a consistent BMR level for RfD calculations across studies. Obviously, limitations in the animal bioassays in regard to minimal test doses for evaluation, shallow dose–responses, and use of study designs with widely spaced test doses will limit the utility of these assays for any type of quantitative assessments, whether NOAEL- or BMD-based approaches.

Nonthreshold Approaches—As Figure 4–3 shows, numerous dose–response curves can be proposed in the low-dose region of the dose–response curve if a threshold assumption is not made. Because the risk assessor generally needs to extrapolate beyond the region of the dose–response curve for which experimentally observed data are available, the choice of models to generate curves in this region has received lots of attention. For nonthreshold responses, methods for dose–response assessments have also utilized models for extrapolation to de minimus (10^{-4} to 10^{-6}) risk levels at very low doses, far below the biologically observed response range and far below the effect levels evaluated for threshold responses.

Statistical or Probability Distribution Models—Two general types of dose–response models exist: statistical (or probability distribution models) and mechanistic models. The distribution models are based on the assumption that each individual has a tolerance level for a test agent and that this response level is a variable following a specific probability distribution function. These responses can be modeled using a cumulative dose–response function. However, extrapolation of the experimental data from 50% response levels to a "safe," "acceptable," or "de minimus" level of exposure—e.g., one in a million risk above background—illustrates the huge gap between scientific observations and highly protective risk limits (sometimes called virtually *safe* doses, or those corresponding to a 95% upper confidence limit on adverse response rates).

Models Derived from Mechanistic Assumptions—This modeling approach designs a mathematical equation to describe dose–response relationships that are consistent with postulated biological mechanisms of response. These models are based on the idea that a response (toxic effect) in a particular biological unit (animal or human) is the result of the random occurrence of one or more biological events (stochastic events).

Radiation research has spawned a series of "hit models" for cancer modeling, where a hit is defined as a critical cellular event that must occur before a toxic effect is produced. The simplest mechanistic model is the one-hit (one-stage) linear model in which only one hit or critical cellular interaction is required for a cell to be altered. As theories of

cancer have grown in complexity, multi-hit models have been developed that can describe hypothesized single-target multi-hit events, as well as multi-target, multi-hit events in carcinogenesis.

Toxicologic Enhancements of the Models—Three exemplary areas of research that have improved the models used in risk extrapolation are time to tumor information, physiologically based toxicokinetic modeling (described in Chapter 7), and biologically based dose–response (BBDR) modeling. The BBDR model aims to make the generalized mechanistic models discussed in the previous section more clearly reflect specific biological processes. Measured rates are incorporated into the mechanistic equations to replace default or computer-generated values.

Development of BBDR models for end points other than cancer is limited; however, several approaches have been explored in developmental toxicity utilizing mode of action information on cell cycle kinetics, enzyme activity, litter effects, and cytotoxicity as critical end points. Approaches have been proposed that link pregnancy-specific toxicokinetic models with temporally sensitive toxicodynamic models for developmental impacts. Unfortunately, the lack of specific, quantitative biological information for most toxicants and for most end points limits study and utilization of these models.

EXPOSURE ASSESSMENT

The primary objectives of exposure assessment are to determine source, type, magnitude, and duration of contact with the agent of interest. Obviously, a critical element of the risk assessment process requires recognition that hazard does not occur in the absence of exposure. However, exposure data are frequently identified as the key area of uncertainty in overall risk determination. The primary goal of using exposure information in quantitative risk assessment is not only to determine the type and amount of total exposure, but also to find out specifically how much may be reaching target tissues. A key step in making an exposure assessment is determining what exposure pathways are relevant for the risk scenario under development. The subsequent steps entail quantitation of each pathway identified as a potentially relevant exposure and then summarizing these pathway-specific exposures for calculation of overall exposure.

Additional considerations for exposure assessments include how time and duration of exposures are evaluated in risk assessments. In general, estimates for cancer risk use averages over a lifetime. In a few cases, short-term exposure limits (STELs) are required and characterization of brief but high levels of exposure is significant. In these cases exposures are not averaged over the lifetime and the effects of high, short-term doses are estimated. With developmental toxicity, a single exposure can be sufficient to produce an adverse developmental effect if exposures occur during a window of developmental susceptibility; thus, daily doses are used, rather than lifetime weighted averages.

RISK CHARACTERIZATION

Variation in Susceptibility

Toxicology has been slow to recognize the marked variation among humans. Generally, assay results and toxicokinetic modeling utilize means and standard deviations to measure variation, or even standard errors of the mean, thereby ignoring variability in response due to differences in age, sex, health status, and genetics.

One key challenge for risk assessment will be interpretation and linking of observations from highly sensitive molecular and genome-based methods with the overall process of toxicity. Biomarkers of early effects, like frank clinical pathology, arise as a function of exposure, response, and time. Early, subtle, and possibly reversible effects can generally be distinguished from irreversible disease states.

The challenge for interpretation of early and highly sensitive response biomarkers is made clear in the analysis of data from gene expression arrays. Because our relatively routine ability to monitor gene responses has grown exponentially in the last decade, the need for toxicologists to interpret such observations for risk assessment and the overall process of toxicity has increased with equal or greater intensity.

Microarray analysis for risk assessment requires sophisticated analyses to arrive at a functional interpretation and linkage to a conventional toxicologic end point. Because of the vast number of measured responses with gene expression arrays, pattern analysis techniques are being used. The extensive databases across chemical classes, pathological conditions, and stages of disease progression that are essential for these analyses are being developed.

INFORMATION RESOURCES

Though numerous information resources are available for risk assessment, a few are listed below in order to provide the reader with examples of risk assessment resources and databases. The Toxicology Data Network (TOXNET) from the National Library of Medicine (http://toxnet.nlm.nih.gov/) provides access to databases on toxicology, hazardous chemicals, and related areas. These information sources vary in the included level of assessment, ranging from just listings of scientific references without comment to extensive peer-reviewed risk assessment information. The World Health Organization (http://who.int/) provides chemical-specific information through the International Programme on Chemical Safety (http://who.int/pcs/IPCS/index.htm) criteria documents and health and safety documents. The International Agency for Research on Cancer (IARC) provides data on specific classes of carcinogens as well as individual agents. The National Institute of Environmental Health Sciences (NIEHS) National Toxicology Program provides technical reports on the compounds tested as a part of this national program (http://ntp.niehs.nih.gov/).

Recently, new toxicogenomic databases that identify and, in some cases, provide characterization of chemicals have become available. The National Center for Biotechnology

Information (NCBI) provides access to an enormous set of biomedical and genomic information which can be valuable for risk assessment, and they have worked to incorporate toxicologically relevant end points. ACToR (http://actor.epa.gov/actor/faces/ACToRHome.jsp), the EPA's online database on chemical toxicity data and potential chemical risks to human health and the environment, is another useful resource for risk assessments. The Comparative Toxicogenomics Database (http://ctd.mdibl.org/) includes data describing cross-species chemical–gene–protein interactions and chemical–gene–disease relationships which illuminate molecular mechanisms underlying variable susceptibility and environmentally induced diseases. Although these databases provide useful hazard identification and mechanistic information, there is little emphasis on exposure data.

RISK PERCEPTION AND COMPARATIVE ANALYSES OF RISK

Individuals respond very differently to information about hazardous situations and products, as do communities and whole societies. Understanding these behavioral responses is critical in stimulating constructive risk communication and evaluating potential risk management options. In a classic study, students, League of Women Voters members, active club members, and scientific experts were asked to rank 30 activities or agents in order of their annual contribution to deaths. Club members ranked pesticides, spray cans, and nuclear power as safer than did other lay persons. Students ranked contraceptives and food preservatives as riskier and mountain climbing as safer than did others. Experts ranked electric power, surgery, swimming, and X-rays as more risky and nuclear power and police work as less risky than did lay persons. There are also group differences in perceptions of risk from chemicals among toxicologists, correlated with their employment in industry, academia, or government.

Psychological factors such as dread, perceived uncontrollability, and involuntary exposure interact with factors that represent the extent to which a hazard is familiar, observable, and "essential" for daily living. Figure 4–5 presents a grid on the parameters controllable/uncontrollable and observable/not observable for a large number of risky activities; for each of the two paired main factors, highly correlated factors are described in the boxes.

Public demand for government regulations often focuses on involuntary exposures (especially in the food supply, drinking

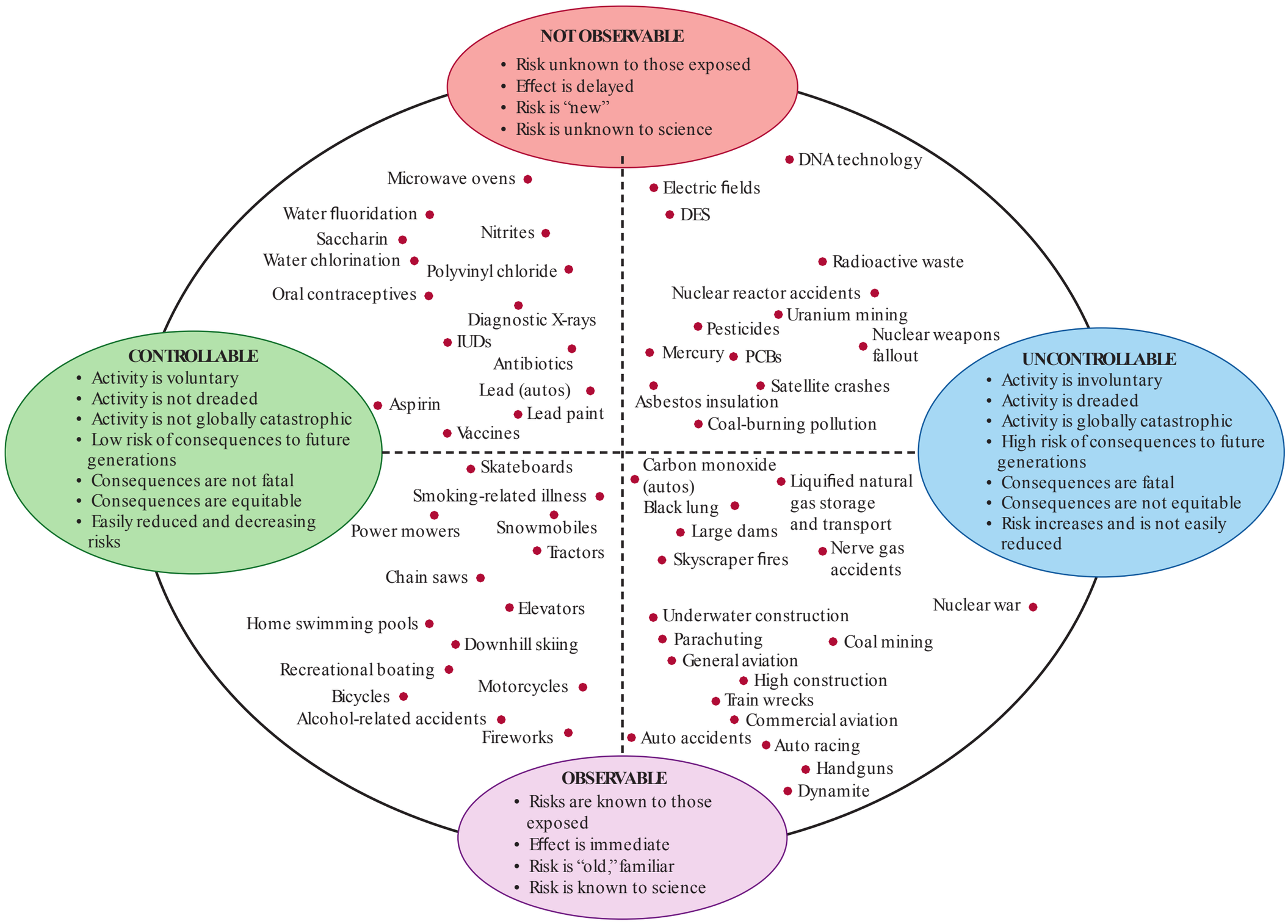

FIGURE 4–5 **Perceptions of risk illustrated using a "risk space" axis diagram.** Risk space has axes that correspond roughly to a hazard's perceived "dreadedness" and to the degree to which it is familiar or observable. Risks in the upper right quadrant of this space are most likely to provoke calls for government regulation.

water, and air) and unfamiliar hazards, such as radioactive waste, electromagnetic fields, asbestos insulation, and genetically modified crops and foods. Many people respond very negatively when they perceive that information about hazards or even about new technologies without reported hazards has been withheld by the manufacturers (genetically modified foods) or by government agencies (HIV-contaminated blood transfusions in the 1980s; extent of hazardous chemical or radioactive wastes).

Most people regularly compare risks of alternative activities—on the job, in recreational pursuits, in interpersonal interactions, and in investments. Determining how best to conduct comparative risk analyses has proved difficult due to the great variety of health and environmental benefits, the gross uncertainties of dollar estimates of benefits and costs, and the different distributions of benefits and costs across the population.

EMERGING CONCEPTS

There is a need to ensure that the risk question(s) is(are) succinctly framed to answer questions in the real world. Environmental health is very dynamic and many divergent emerging environmental challenges such as climate change, energy shortages, and engineered nanoparticles will require an expansion of our context well beyond single-chemical, single-exposure scenarios. In order to accomplish this goal, global and international thinking will be required.

Well-being is increasingly being used to describe human health and the goal of sustainable environmental risk management. Well-being goes beyond "disease-free" existence to freedom from want (including food and water security) and fear (personal safety) and sustainable futures. Recognition that environmental problems are global is essential to how we manage risks and address sustainability. Research and development efforts must examine chemical safety for sustainable and healthy communities with safe and sustainable water, air, and energy resources.

PUBLIC HEALTH RISK MANAGEMENT

Associated with concepts of well-being and sustainability is a public health orientation to use toxicological tests to identify and characterize potential health risks and to prevent the unsafe use of such agents. There are three stages of prevention: primary, whose goal is prevention and risk or hazard avoidance; secondary, whose goal is mitigation or preparedness including risk or vulnerability reduction and risk transfer; and tertiary, where prompt response or recovery is an approach for decreasing residual risk or risk reduction. Figure 4–5 shows an overview of risk assessment and management for public health where concepts of capacity assessment, vulnerability, and impact assessment are included. In this context, vulnerability assessment would include consideration of exposure and susceptibility as part of the vulnerability assessment. Hazard analysis refers to both hazard identification and probability-based frequency of anticipated events. Capacity assessment has been used for identifying strengths and resiliency of a system to impact.

SUMMARY

Risk assessment objectives vary with the issues, risk management needs, and statutory requirements. Hence, setting the context and problem formation for risk evaluation is essential. The frameworks are sufficiently flexible to address various objectives and to accommodate new knowledge while providing guidance for priority setting in industrial, environmental, governmental, and public health agencies. Risk assessment analyzes the science, identifies uncertainty and provides approaches for decisions. Toxicology, epidemiology, exposure assessment, and clinical observations can be linked with biomarkers, cross-species investigations of mechanisms of effects, and systematic approaches to risk assessment, risk communication, and risk management. Advances in toxicology are certain to improve the quality of risk assessments as scientific findings substitute data for assumptions and help to describe and model uncertainty more credibly.

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QUESTIONS

1. Which of the following is NOT important in hazard identification?
   a. structure–activity analysis.
   b. in vitro tests.
   c. animal bioassays.
   d. susceptibility.
   e. epidemiology.

2. The probability of an adverse outcome is defined as:
   a. hazard.
   b. exposure ratio.
   c. risk.
   d. susceptibility.
   e. epidemiology.

3. The systematic scientific characterization of adverse health effects resulting from human exposure to hazardous agents is the definition of:
   a. risk.
   b. hazard control.
   c. risk assessment.
   d. risk communication.
   e. risk estimate.

4. Which of the following is not an objective of risk management?
   a. setting target levels for risk.
   b. balancing risks and benefits.
   c. calculating lethal dosages.
   d. setting priorities for manufacturers.
   e. estimating residual risks.

5. Which of the following is NOT a feature in the design of standard cancer bioassays?
   a. more than one species.
   b. both sexes.
   c. near lifetime exposure.
   d. approximately 50 animals per dose group.
   e. same dose level for all groups.

6. Which of the following types of epidemiologic study is always retrospective?
   a. cohort.
   b. cross-sectional.
   c. case–control.
   d. longitudinal.
   e. exploratory.

7. Which of the following is defined as the highest nonstatistically significant dose tested?
   a. ED_{50}
   b. ED_{100}
   c. NOAEL.
   d. ADI.
   e. COAEL.

8. Which of the following represents the dose below which no additional increase in response is observed?
   a. ED_{10}
   b. LD_{10}
   c. RfC.
   d. threshold.
   e. significance level.

9. Which of the following is NOT needed to calculate the reference dose using the BMD method?
   a. MF.
   b. percent benchmark response.
   c. NOAEL.
   d. UF.
   e. benchmark dose.

10. Virtually safe doses are described at which confidence level?
    a. 90%.
    b. 95%.
    c. 99%.
    d. 99.9%.
    e. 99.99%.