Human Health Risk Assessment

RONALD E. BAYNES

24.1 INTRODUCTION

We often perform toxicological research to better understand the mechanism and associated health risk following exposure to hazardous agents. Risk assessment is a systematic scientific characterization of potential *adverse health effects* following exposure to these hazardous agents. Risk assessment activities are designed to *identify, describe*, and *measure qualities and quantities* from these toxicological studies, which are often conducted with homogeneous animal models at doses and exposure duration not encountered in a more heterogeneous human population. Herein lie the challenge of risk assessment. The use of default assumptions because of some level of uncertainty in our extrapolations across species, doses, routes, and interindividual variability, the risk assessment process is often perceived as lacking scientific rigor. This chapter will cover traditional practices as well as new and novel approaches that utilize more of the available scientific data to identify and reduce uncertainty in the process. The advent of powerful computers and sophisticated software programs has allowed the development of quantitative models that better describe the dose-response relationship, refine biologically relevant dose estimates in the risk assessment process, and encourage departure from traditional default approaches (Conolly et al., 1999). Although the focus of this chapter is on current and novel risk assessment methods that are scientifically based, it is critical that the reader be aware of the differences between risk assessment and risk management, which are summarized in Table 24.1.

Results from the risk assessment are used to inform *risk management*. The risk manager uses the risk information in conjunction with factors such as the social importance of the risk, the social acceptability of the risk, the economic impacts of risk reduction, engineering, and legislative mandates when deciding on and implementing risk management approaches.

The risk assessment may be perceived as the source of a risk management decision, when in fact, social concerns, international issues, trade, public perception, or other non-risk considerations may be taken into consideration. Finally there is one activity known as *risk communication* that involves making the risk assessment and risk

A Textbook of Modern Toxicology, Third Edition, edited by Ernest Hodgson
ISBN 0-471-26508-X

Table 24.1 Comparison of Risk Assessment and Risk Management Activities

Risk Assessment	Risk Management
Nature of effects	Social importance of risk
Potency of agent	Acceptable risk
Exposure	Reduce/not reduce risk
Population at risk	Stringency of reduction
Average risk	Economics
High-end risk	Priority of concern
Sensitive groups	Legislative mandates
Uncertainties of science	Legal issues
Uncertainties of analysis	Risk perception
Identify	*Evaluate*
Describe	*Decide*
Measure	*Implement*

management information comprehensible to lawyers, politicians, judges, business and labor, environmentalists, and community groups.

24.2 RISK ASSESSMENT METHODS

According to the National Research Council of the National Academy of Science, risk assessment consists of four broad but *interrelated* components: hazard identification, dose-response assessment, exposure assessment, and risk characterization, as depicted in Figure 24.1. The reader should, however, be aware that these risk assessment activities can provide research needs that improve the accuracy of estimating the "risk" or probability of an adverse outcome.

24.2.1 Hazard Identification

In this first component of risk assessment, the question of causality in a qualitative sense in addressed; that is, the degree to which evidence suggests that an agent elicits

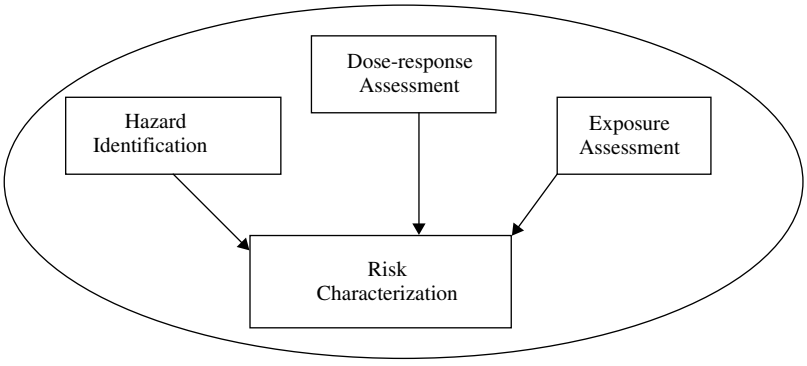

Figure 24.1 Risk assessment paradigm as per NAS and US EPA.

a given effect in an exposed population. Among many factors the quality of the studies and the severity of the health effects should be evaluated at this stage. The following are evaluated: (1) validity of the toxicity data, (2) weight-of-evidence summary of the relationship between the substance and toxic effects, and (3) estimates of the generalizability of data to exposed populations. Where there are limited in vivo toxicity data, *structural activity relationships* (SARs) and *short-term assays* may be indicative of a chemical hazard. Key molecular structures such as *n*-nitroso or aromatic amine groups and azo dye structures can be used for prioritizing chemical agents for further testing. SARs are useful in assessing relative toxicity of chemically related compounds, but there are several limitations. For example, toxicity equivalent factors (TEFs) based on induction of Ah receptor by dioxins demonstrated that SARs may not always be predictive. In vitro short-term inexpensive test such as bacterial mutation assays can help *identify* carcinogens, and there are other short-term tests that can help identify chemicals that potentially can be associated with neurotoxicity, developmental effects, or immunotoxicity. Many of these in vitro studies can provide some insight into mechanism(s) of action, but there may be some *false positives* and *false negatives*. Animal studies are usually route-specific and relevant to human exposure, and animal testing usually involves two species, both sexes, 50 animals/dose group, and near-lifetime exposures. Doses are usually 90, 50, and 10 to 25% of the maximum tolerated dose (MTD). In carcinogenicity studies, the aim is to observe significant increases in number of tumors, induction of rare tumors, and earlier induction of observed tumors. However, rodent bioassays may not be predictive of human carcinogenicity because of mechanistic differences For example, renal tumors in male rats is associated with $\alpha_{2\mu}$-globulin-chemical binding and accumulation leading to neoplasia; however, $\alpha_{2\mu}$-globulin is not found in humans, mice, or monkeys. There are differences in susceptibility to aflatoxin-induced tumors between rats and mice that can be explained by genetic differences in expression of cytochrome P450 and GST isoenzymes. Whereas humans may be as sensitive as rats to AFB_1-induced liver tumors, mice may not be predictive of AFB_1-induced tumors in humans. Epidemiological data from human epidemiological studies are the most convincing of an association between chemical exposure and disease, and therefore can very useful for hazard identification. Exposures are not often well defined and retrospective, and confounding factors such as genetic variations in a population and human lifestyle differences (e.g., smoking) present a further challenge. The three major types of epidemiological studies available are (1) *cross-sectional studies*, which involve sampling without regard to exposure or disease status, and these studies identify risk factors (exposure) and disease but not useful for establishing cause-effect relationships; (2) *cohort studies*, which involve sampling on the basis of exposure status, and they target individuals exposed and unexposed to chemical agent and monitored for development of disease, and these are *prospective studies*; (3) *case-control studies*, which involve sampling on the basis of disease status. These are retrospective studies, where diseased individuals are matched with disease-free individuals.

24.2.2 Exposure Assessment

This process is an integral part of the risk assessment process. However this will be introduced only briefly in this chapter, and the reader is encouraged to consult Chapter 28 in this text as well as numerous other texts that describe the process in

more depth. In brief, exposure assessment attempts to identify potential or completed exposure pathways resulting in contact between the agent and at-risk populations. It also includes demographic analysis of at-risk populations describing properties and characteristics of the population that potentiate or mitigate concern and description of the magnitude, duration, and frequency of exposure. The reader should be aware that exposure may be aggregate (single event added across all media) and/or cumulative (multiple compounds that share a similar mechanism of toxicity). Various techniques such as biomonitoring, model development, and computations can be used to arrive at an estimate of chemical dose taken up by humans, that is, chemical exposure. For example, the lifetime average daily dose (LADD) is a calculation for individuals exposed at levels near the middle of the exposure distribution:

$$\text{LADD} = \frac{(\text{Conc. in media}) \times (\text{Contact rate}) \times (\text{Contact fraction}) \times (\text{Exposure duration})}{(\text{Body weight}) \times (\text{Lifetime})}.$$

Biological monitoring of blood and air samples represent new ways of reducing uncertainty in these extrapolations. For occupational exposures there are occupational exposure limits (OELs) that are guidelines or recommendations aimed at protecting the worker over their entire working lifetime (40 years) for 8 h/day, 5 days/week work schedule. Most OELs are presented as a time-weighted average concentration for an 8-hour day for a 40-hour work week. There are threshold limit values (TLVs) that refer to airborne concentrations and conditions under which workers may be exposed daily but do not develop adverse health effects. The short-term exposure limit (STEL) are recommended when exposures are of short duration to high concentrations known to cause acute toxicity.

24.2.3 Dose Response and Risk Characterization

Dose response is a quantitative risk assessment process, and primarily involves characterizing the relationship between chemical potency and incidence of adverse health effect. Approaches to characterizing dose-response relationships include effect levels such as LD50, LC50, ED50, no observed adverse effect levels (NOAELs), margins of safety, therapeutic index. The dose-response relationship provides an estimation of the relationship between the dose of a chemical agent and incidence of effects in a population. Intuitively, a steep dose-response curve may be indicative of a homogeneous population response, while less steep or almost flat slope may be indicative of greater distribution in response. In extrapolating from relatively high levels of exposure in experimental exposures (usually animals) to significantly lower levels that are characteristic of the ambient environment for humans, it is important to note the shape of the dose-response function below the experimentally observable range and therefore the range of inference. The shape of the slope may be linear or curvilinear and, it should be noted that the focus of risk assessment is generally on these lower regions of the dose-response curve (Figure 24.2).

There is a class of curvilinear dose-response relationships in toxicological and epidemiological studies that may be described as *U-shaped* or *J-shaped curves*. Other terms such as biphasic, and more recently *hormesis*, have been used to refer to paradoxical effects of low-level toxicants. In brief, these dose-response curves reflect an apparent improvement or reversal in the effect of an otherwise toxic agent. These

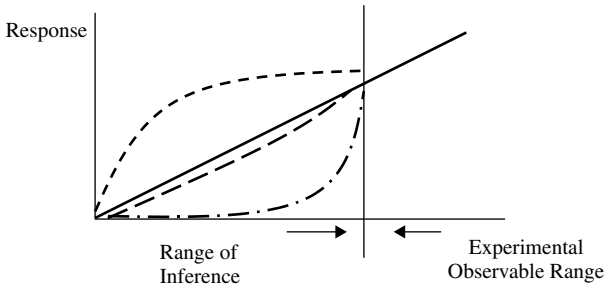

Figure 24.2 Dose-response curve, with emphasis on the shape of the dose-response function below the experimentally observable range and therefore the range of inference where people are realistically exposed.

U-shaped effects can be explained in terms of homeostatic adjustments or overcorrections in the operation of feedback mechanisms. Examples of studies with data fitting a U-shaped curve include the hormetic effect of organic lead on body growth in rats (Cragg and Rees, 1984) and peripheral nerve conduction velocity in children at low doses (Ewert et al., 1986). Similar relationships have been observed with alcohol and nicotine in humans. It has been proposed that because thresholds are inherent in U-shaped dose-response curves, the linear no-threshold extrapolation method is not an appropriate approach for regulating hormetic agents. The current risk assessment paradigm used by US EPA and other federal agencies does not conflict with the concept of hormesis, but it has been proposed that the risk assessor's analyzes make an active consideration of the data and the application of that data in the low dose portion of the dose-response curve for hormetic agents.

24.3 NONCANCER RISK ASSESSMENT

The noncancer risk assessment process assumes a *threshold*. For many noncarcinogenic effects, protective mechanisms are believed to exist that must be overcome before an adverse effect is manifested. At the cellular level for some toxicant, a range of exposures exists from zero to some finite value that can be tolerated by the organism with essentially no chance of expression of adverse effects. The aim here in risk assessment is to identify the upper bound of this tolerance range (i.e., the maximum subthreshold level). This approach involves obtaining the no observed adverse effect level. NOAEL is the highest dose level that *does not produce a significant* elevated increase in an adverse response. Significance refers to biological and statistical criteria and is dependent on dose levels tested, number of animals, background incidence in the unexposed control groups. Sometimes there is insufficient data to arrive at a NOAEL, and a LOAEL (lowest observed adverse effect level) is derived. The NOAEL is the key datum obtained from the study of the dose-response relationship. The NOAEL is used to calculate reference doses (RfD) for chronic oral exposures and reference concentrations (RfC) for chronic inhalation exposures as per EPA. Other agencies, such as the ATSDR and WHO, use the NOAEL to calculate *minimum risk levels* (MRLs) and *acceptable daily intakes* (ADI). The US EPA describes the RfD as an estimate, with uncertainty spanning an order of magnitude, of a daily exposure to the human population, including

sensitive subgroups, that is likely to be without appreciable deleterious effects during a lifetime. In deriving reference doses, ADIs, or MRLs, the NOAEL is divided by uncertainty factors (UF) as per EPA (EPA, 1989) and ATSDR (ATSDR, 1993) and by modifying factors (MF) as per EPA:

$$\text{RfD} = \frac{\text{NOAEL}}{(\text{UF} * \text{MF})}, \qquad \text{US EPA;}$$

$$\text{MRL} = \frac{\text{NOAEL}}{\text{UF}}, \qquad \text{ATSDR.}$$

The calculated RfD or RfC is based on the selected critical study and selected critical end point. The risk assessor may obtain numerous studies where the toxicant may have more than one toxic end point, and thus there may be many NOAELs to choose from the literature. In some instances poor data quality may be used to exclude those end points from consideration. Also at issue is the determining what is considered an adverse effect, and this has been summarized with a few examples in Table 24.2. In sum, the MRL or RfD is based on the less serious effects and no serious effects. The following are example effects not used in obtaining a NOAEL: decrease in body weight less than 10%, enzyme induction with no pathologic changes, changes in organ weight with no pathologic changes, increased mortality over controls that is not significant ($p > 0.05$), and hyperplasia or hypertrophy with or with out changes in organ weights.

24.3.1 Default Uncertainty and Modifying Factors

Most extrapolations from animal experimental data in the risk assessments require the utilization of uncertainty factors. This is because we are not certain how to extrapolate across species, with species for the most sensitive population, and across duration. To account for variations in the general population and to protect sensitive subpopulations, an uncertainty factor of 10 is used by EPA and ATSDR. The value of 10 is derived from a threefold factor for differences in toxicokinetics and for threefold factor for toxicodynamics. To extrapolate from animals to humans and account for interspecies variability between humans and other mammals, an uncertainty factor of 10 is used by EPA and ATSDR, and as with intraspecies extrapolations, this 10-fold factor is assumed to be associated with in toxicodynamics and toxicokinetics. An uncertainty

Table 24.2 Comparison of Less Serious Effects and Serious Effects

Less Serious	Serious
Reversible cellular changes	Death
Necrosis, metaplasia, or atrophy	Cancer
	Clinically significant organ impairment
Delayed ossifciation	Visceral or skeletal abnormalities
Alteration in offspring weight	Cleft palate, fused ribs
Altered T-cell activity	Necrosis inn immunologic components
Auditory disorders	Visual disorders
50% Reduction in offspring	Abnormal sperm

factor of 10 is used when a NOAEL derived from a subchronic study instead of a chronic study is used as the basis for a calculation of a chronic RfD (EPA only). Note that ATSDR does not perform this extrapolation but derive chronic and subchronic MRLs. An uncertainty factor of 10 is used in deriving an RfD or MRL from a LOAEL when a NOAEL is not available. It should be noted that there are no reference doses for dermal exposure, however when there is insufficient dermal absorption data, the EPA uses a default factor of 10% to estimate bioavailability for dermal absorption. A modifying factor ranging from 1 to 10 is included by EPA only to reflect a qualitative professional assessment of additional uncertainties in the critical study and in the entire data base for the chemical not explicitly addressed by preceding uncertainty factors.

Refinements of the RfC have utilized mechanistic data to modify the interspecies uncertainty factor of 10 (Jarabek, 1995). The reader should appreciate that with the inhalation route of exposure, dosimetric adjustments are necessary and can affect the extrapolations of toxicity data of inhaled agents for human health risk assessment. The EPA has included dosimetry modeling in RfC calculations, and the resulting dosimetric adjustment factor (DAF) used in determining the RfC is dependent on physiochemical properties of the inhaled toxicant as well as type of dosimetry model ranging from rudimentary to optimal model structures. In essence, the use of the DAF can reduce the default uncertainty factor for interspecies extrapolation from 10 to 3.16.

The 1996 Food Quality Protection Act (FQPA) now requires that an additional safety factor of 10 be used in the risk assessment of pesticides to ensure the safety of infants and children, unless the EPA can show that an adequate margin of safety is assured with out it (Scheuplein, 2000). The rational behind this additional safety factor is that infants and children have different dietary consumption patterns than adults and infants, and children are more susceptible to toxicants than adults. We do know from pharmacokinetics studies with various human pharmaceuticals that drug elimination is slower in infants up to 6 months of age than in adults, and therefore the potential exists for greater tissue concentrations and vulnerability for neonatal and postnatal effects. Based on these observations, the US EPA supports a default safety factor greater or less than 10, which may be used on the basis of reliable data. However, there are few scientific data from humans or animals that permit comparisons of sensitivities of children and adults, but there are some examples, such as lead, where children are the more sensitive population. It some cases qualitative differences in age-related susceptibility are small beyond 6 months of age, and quantitative differences in toxicity between children and adults can sometimes be less than a factor of 2 or 3.

Much of the research efforts in risk assessment are therefore aimed at reducing the need to use these default uncertainty factors, although the risk assessor is limited by data quality of the chemical of interest. With sufficient data and the advent of sophisticated and validated physiologically based pharmacokinetic models and biologically based dose-response models (Conolly and Butterworth, 1995), these default values can be replaced with science-based factors. In some instances there may be sufficient data to be able to obtain distributions rather than point estimates.

24.3.2 Derivation of Developmental Toxicant RfD

Developmental toxicity includes any detrimental effect produced by exposures during embryonic development, and the effect may be temporary or overt physical malformation. Adverse effects include death, structural abnormalities, altered growth, and

functional deficiencies. Maternal toxicity is also considered. The evidence is assessed and assigned a weight-of-evidence designation as follows: category A, category B, category C, and category D. The scheme takes into account the ratio of minimum maternotoxic dose to minimum teratogenic dose, the incidence of malformations and thus the shape of the dose-response curve or dose relatedness of the each malformation, and types of malformations at low doses. A range of uncertainty factors are also utilized according to designated category as follows: category A = 1–400, category B = 1–300, category C = 1–250, and category D = 1–100. Developmental RfDs are based a short duration of exposure and therefore cannot be applied to lifetime exposure.

24.3.3 Determination of RfD and RfC of Naphthalene with the NOAEL Approach

The inhalation RfC for naphthalene was 0.003 mg/m^3, and this RfC was derived from a chronic (2-year) NTP inhalation study in mice using exposures of 0, 10, or 30 ppm (NTP, 1992). Groups of mice were exposed for 5 days a week and 6 hours a day. This study identified a LOAEL of 10 ppm. A dose-related incidence of chronic inflammation of the epithelium of the nasal passages and lungs was observed. This LOAEL concentration was normalized by adjusting for the 6-hour-per-day and 5-day-per-week exposure pattern. A LOAEL of 9.3 mg/m3 was obtained was derived by converting 10 ppm first to mg/m^3 and then duration-adjusted levels for 6 h/day and 5 days/week for 103 weeks. An UF of 3000 was used, where 10 was for the interspecies (mice to humans) extrapolations, 10 for intraspecies variation in humans, 10 for using a LOAEL instead of a NOAEL, and 3 for database deficiencies.

The oral RfD for naphthalene was 0.02 mg/kg/day, and a study by Battelle (1980) was used to calculate the RfD. Decreased body weight was the most sensitive end point in groups of Fischer 344 rats given 0, 25, 50, 100, 200, or 400 mg/kg for 5 days/week for 13 weeks. These doses were also duration-adjusted to 0, 17.9, 35.7, 71.4, 142.9, and 285.7 mg/kg/day, respectively. The NOAEL for $a > 10\%$ decrease in body weight in this study was 71 mg/kg/day. The UF of 3000 was based on 10 for rats to humans extrapolation, 10 for human variation, 10 to extrapolate from subchronic to chronic, and 3 for database deficiencies including lack of chronic oral exposure studies.

24.3.4 Benchmark Dose Approach

There are several problems associated with using the NOAEL approach to estimate RfDs and RfCs. The first obvious constraint is that the NOAEL must by definition be one of the experimental doses tested. Once this dose is identified, the rest of the dose-response curve is ignored. In some experimental designs where there is no identifiable NOAEL but LOAEL, the dose-response curve is again ignored, and the NOAEL is derived by application of uncertainty factors as described earlier. This NOAEL approach does not account for the variability in the estimate of the dose response, and furthermore experiments that test fewer animals result in larger NOAELs and thus larger RfDs and RfCs.

An alternative approach known as the benchmark dose (BMD) approach has been developed and implemented by risk assessors as an alternative to the NOAEL approach to estimate RfDs and RfCs. This approach is not constrained by experimental design

as the NOAEL approach, and it incorporates information on the sample size and shape of the dose-response curve. In fact this approach can be used for both threshold and nonthreshold adverse effects as well as continuous and quantal data sets. This requires use of Benchmark Dose Software where the dose-response is modeled and the lower confidence bound for a dose at a specified response level (benchmark response) is calculated. The benchmark response is usually specified as a 1–10% response; that is, it corresponds to a dose associated with a low level of risk such as 1–10%.

Figure 24.3 shows how an effective dose that corresponds to a specific change of effect/response (e.g., 10%) over background and a 95% lower confidence bound on the dose is calculated. The latter is often referred to as the BMDL or LBMD, as opposed to the BMD, which does not have this confidence limited associated with it.

Because the benchmark represents a statistical lower limit, larger experiments will tend, on average, to give larger benchmarks, thus rewarding good experimentation. This is not the case with NOAELs, as there is an inverse relationship between NOAEL and size of experiments. For example, poorer experiments possessing less sensitivity for detecting statistically significant increases in risk inappropriately result in higher NOAELs and RfDs, which may have an unknown unacceptable level of risk. In essence, the NOAEL is very sensitive to sample size, and there can also be high variability between experiments. With the benchmark dose approach, all the doses and slopes of the curve influence the calculations, variability of the data is considered, and the BMD is less variable between experiments. In the BMD approach quantitative toxicological data such as continuous data (organ weights serum levels, etc.) and quantal or incidence data (pathology findings, genetic anomalies, etc.) are fitted to numerous dose-response models described in the literature. The resulting benchmark dose that, for example, corresponds to a tumor risk of 10% generally can be estimated with adequate precision and not particularly dependent on the dose-response model used to fit the data. Note that dose intervals are not required for BMD estimation. This will be greatly appreciated in the cancer risk assessment section of this chapter.

24.3.5 Determination of BMD and BMDL for ETU

The BMD method has been quite extensively in assessing quantal data, and very often this has involved analysis of data from developmental and reproductive toxicity

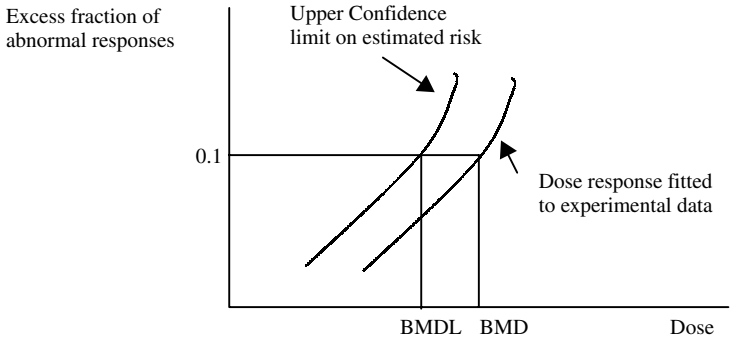

Figure 24.3 Benchmark dose determination from dose response relationship with the BMDL corresponding to the lower end of a one-sided 95% confidence interval for the BMD.

studies. In this study example (Crump, 1984), rats were exposed to ethylenethiourea (ETU) at 0, 5, 10, 20, 40, and 80 mg/kg doses, and the number affected with fetal anomalies per number of rats were 0/167, 0/132, 1/138, 14/81, 142/178, and 24/24, respectively. The benchmark dose computation can involve utilization of any given dose-response probability model, but in this example the quantal Weibull model was used and the specified effect was set at 0.01 (1%) with confidence level of 0.95. The BMD was determined to be 8.9 mg/kg, and the BMDL was 6.9 mg/kg. This value is close to the NOAEL, which is 5 mg/kg, but it does demonstrate that the NOAEL approximates a lower confidence limit on the BMD corresponding to an excess risk of about 1% for proportions of fetal anomalies. In fact an empirical analysis of some 486 developmental toxicity studies has demonstrated that the NOAEL can result in an excess risk of 5% for proportions of dead or malformed fetuses per litter. The reader should at this stage recognize that the BMD approach can also be used in cancer risk assessment as we are often times working with quantal data that are ideally suited for BMD modeling.

24.3.6 Quantifying Risk for Noncarcinogenic Effects: Hazard Quotient

The measure used to describe the potential for noncarcinogenic toxicity to occur is not expressed as the probability. Probabilistic approach is used in cancer RA. For noncancer RA, the potential for noncarcinogenic effects is evaluated by comparing an exposure level (E) over a specified time period with a reference dose (RfD). This ratio is called a hazard quotient:

$$\text{Hazard quotient} = \frac{\text{E}}{\text{RfD}}.$$

In general, the greater the value of E/RfD exceeds unity, the greater is the level of concern. Note that this is a ratio and not to be interpreted as a statistical probability.

24.3.7 Chemical Mixtures

Human populations are more likely to be exposed simultaneously or sequentially to a mixture of chemicals rather than to one single chemical. Standard default approaches to mixture risk assessment consider doses and responses of the mixture components to be additive. However, it should also be recognized that components in the mixture can also result in synergistic, antagonistic, or no toxicological effect following exposure to a chemical mixture. Therefore mixture toxicity cannot always be predicted even if we know the mechanisms of all toxic components in a defined mixture. Furthermore tissue dosimetry can be complicated by interactions at the route of entry (e.g., GIT, skin surface) and clearance mechanisms in the body. In essence, there are considerable uncertainties involved in trying to extrapolate effects following exposure to chemical mixtures. Several PBPK models have been used to quantitate these effects and also provide some information useful for risk assessment of chemical mixtures (Krishnan et al., 1994; Haddad et al. 2001).

The 1996 FQPA has also mandated that the EPA should also consider implementing cumulative risk assessments for pesticides. Cumulative risk assessments usually involve

integration of the hazard and cumulative exposure analysis, and it primarily involves cumulative nonoccupational exposure by multiple routes or pathways to two or more pesticides or chemicals sharing a common mechanism of toxicity.

Calculation procedures differ for carcinogenic and noncarcinogenic effects, but both sets of procedures *assume dose additivity* in the absence of information on mixtures:

$$\text{Cancer risk equation for mixtures}: \quad \text{Risk}_\text{T} = \Sigma\text{Risk}_\text{I},$$

$$\text{Noncancer hazard index} = \frac{\text{E}_1}{\text{RfD}_1} + \frac{\text{E}_2}{\text{RfD}_2} + \cdots + \frac{\text{E}_i}{\text{RfD}_\text{i}}.$$

This hazard index (HI) approach as well as other indexes (e.g., relative potency factors) are applied for mixture components that induce the same toxic effect by identical mechanism of action. In cases where there are different mechanisms, separate HI values can be calculated for each end point of concern. As the equation above indicates, the HI is easy to calculate, as there is simply scaling of individual component exposure concentrations by a measure of relative potency such as the RfD or RfC, and adding scaled concentrations to get an indicator of risk from exposure to the mixture of concern. However, as noted above, this additivity approach does not take into account tissue dosimetry and pharmacokinetic interactions. Recent published risk assessments have utilized mixture PBPK models to account for multiple pharmacokinetic interactions among mixture constituents. These interaction-based PBPK models can quantify change in tissue dose metrics of chemicals during exposure to mixtures and thus improve the mechanistic basis of mixture risk assessment. Finally the reader should be aware that this HI is different from the a term known as the margin of safety (MOS), which is the ratio of the critical or chronic NOAEL for a specific toxicological end point to an estimate of human exposure. MOS values greater than 100 are generally considered protective if the NOAEL is derived from animal data.

24.4 CANCER RISK ASSESSMENT

For cancer risk assessment an assumption is held that a threshold for an adverse effect does not exist with most individual chemicals. It is assumed that a small number of molecular events can evoke changes in a single cell that can lead to uncontrolled cellular proliferation and eventually to a clinical state of disease. This mechanism is referred to as "nonthreshold" because there is believed to be essentially no level of exposure to such a chemical that does not pose a finite probability, however small, of generating a carcinogenic response. That is, no dose is though to be risk free. Therefore, in evaluations of cancer risks, an effect threshold cannot be estimated. For carcinogenic effects, the US EPA uses a two-part evaluation: (1) the substance is first assigned a weight-of-evidence classification and then (2) a slope factor is calculated.

1. Assigning a weight-of-evidence. The aim here is to determine the likelihood that the agent is a human carcinogen. The *evidence* is characterized separately for human studies and animal studies as *sufficient, limited, inadequate, no data*, or *evidence of no effect*. Based on this characterization and on the extent to which the chemical has been shown to be a carcinogen in animals or humans or both, the chemical is given a provisional *weight-of-evidence* classification. The US EPA classification system (EPA,

Table 24.3 Weight of Evidence Designation Based on EPA (1986) Guidelines

Group	Description
A	Human carcinogen
B1 or B2	Probable human carcinogen
C	Possible human carcinogen
D	Not classifiable as to human carcinogenicity
E	Evidence of noncarcinogenicity for humans

Note: B1 indicates that limited human data are available; B2 indicates sufficient evidence in animals and inadequate or no evidence in humans.

1986) shown in Table 24.3 has been revised in the EPA (1996) proposed guidance and more recent draft guidance (EPA, 1999).

This system was also adapted from the approach taken by the International Agency for Research on Cancer (IARC). This alphanumeric classification system has been replaced with a narrative and the following descriptor categories: *known/likely, cannot be determined*, or *not likely*. These EPA (1996) guidelines indicate that not only are tumor findings an important consideration, but also structure-activity relationships, modes of action of carcinogenic agents at cellular or subcellular level and toxicokinetic and metabolic processes. These revised guidelines also indicate that the weighing of evidence should address the conditions under which the agent may be expressed. For example, an agent may "likely" be carcinogenic via inhalation exposure but "not likely" via oral exposure. The narrative will summarize much of this information as well as the mode of action information.

2. Quantifying risk for carcinogenic effects. In the second part of the evaluation, the EPA (1986) guidelines required that quantitative risk be based on the evaluation that the chemical is a known or probable human carcinogen, a toxicity value that defined quantitatively the relationship between dose and response (slope factor) is calculated. Slope factors have been calculated for chemicals in classes A, B1, and B2. Sometimes a value is derived for those in class C on a case-by-case basis. The slope factor is a plausible upper-bound estimate of the probability of a response per unit intake of chemical over a lifetime. Slope factors have been accompanied by the weight-of-evidence classification to indicate the strength of evidence that the chemical is a human carcinogen.

Development of a slope factor entails applying a model to the available data set and using the model to extrapolate from high doses to lower exposure levels expected for human contact. There are a number of low-dose extrapolation models that can be divided into distribution models (e.g., log-probit, Weibull) and mechanistic models (e.g., one-hit, multi-hit, and *linearized multistage*). EPA 1986 guidelines for carcinogen risk assessment are currently being revised, and it is very likely that the new guidelines will encourage the use of biologically based models for cancer risk assessment. The previous guidelines (EPA, 1986) recommended that the linearized multistage model, which is a mechanistic model, be employed in as the default model in most cases. Most of the other models are less conservative. The proposed biologically based models attempt to incorporate as much mechanistic information as possible to arrive at an estimate of slope factors. In essence, after the data are fit to the selected model, the

upper 95th percent confidence limit of the slope of the resulting dose response curve is calculated. *This represents the probability of a response per unit intake over a lifetime*, or that there is a 5% chance that the probability of a response could be greater than the estimated value on the basis of experimental data and model used. In some cases, the slope factors based on human dose-response data are based on "best" estimate instead of upper 95th percent confidence limit. The toxicity values for carcinogenic effects can be expressed in several ways.

The slope factor is expressed as q_1^*:

$$\begin{aligned}\text{Slope factor} &= \text{Risk per unit dose} \\ &= \text{Risk per mg/kg-day.}\end{aligned}$$

The slope factor can therefore be used to calculate the upper bound estimate on risk (R)

$$\text{Risk} = q_1^*[\text{risk} \times (\text{mg/kg/day})^{-1}] \times \text{exposure (mg/kg/day)}.$$

Here risk is a unitless probability (e.g., 2×10^{-5}) of an individual developing cancer and exposure is really chronic daily intake averaged over 70 years: mg/kg/day. This can be determined if we can determine the slope factor and human exposure at the waste site or occupational site. The EPA usually sets a goal of limiting lifetime cancer risks in the range of 10^{-6} to 10^{-4} for chemical exposures, while the FDA typically aims for risks below 10^{-6} for general population exposure. It is therefore quite likely for very high exposures for the accepted EPA range of risk to be exceeded. The EPA range is considered protective of the general and sensitive human population. It should be noted that these orders of magnitude are substantially greater than those used in estimating RfD and RfCs in noncancer risk assessment.

Because relatively low intakes (compared to those experienced by test animals) are most likely from environmental exposure at Superfund hazardous waste sites, it generally can be assumed that the dose-response relationship will be linear on the low-dose portion of the multistage model dose-response curve. The equation above can apply to these linear low-dose situations. This linear equation is valid only at low risk levels (i.e., below the estimated risk of 0.01). For risk above 0.01 the one-hit equation should be used:

$$\text{Risk} = 1 - \exp(\text{-exposure} \times \text{slope factor}).$$

As indicated above, biologically based extrapolation models are the preferred approach for quantifying risk to carcinogens, although it is possible that all the necessary data will not be available for many chemicals. The EPA (1986) guidelines have been modified to include the response data on effects of the agent on carcinogenic processes in addition to data on tumor incidence. Precursor effects and tumor incidence data may be combined to extend the dose response curve below the tumor data; that is, below the range of observation. Thus a biologically based or case-specific dose-response model is developed when there is sufficient data, or a standard default procedure is used when there is insufficient data to adequately curve-fit the data. In brief, the dose-response assessment is considered in two parts or steps, range of observation and range of extrapolation, and the overriding preferred approach is to use the biologically based or case-specific model for both of these ranges. In the first

step of this process, the lower 95% confidence limit on a dose associated with an estimated 10% increase in tumor or nontumor response (LED_{10}) is identified. When human real world exposures are outside the range of the observed or experimental data, this serves as the point of departure or marks the beginning for the extrapolating to these low environmental exposure levels. Note that these procedures are very similar to the benchmark procedure for quantitating risk to noncarcinogenic chemicals. In the second step, the biologically based or case-specific model is preferred for use in extrapolations to lower dose levels provided that there are sufficient data. If the latter is not the case, then default approaches consistent with agent chemical mode of action are implemented with the assumption of linearity or nonlinearity of the dose-response relationship. The linear default approach is a departure from the 1986 guidelines, which used the linearlized multistage (LMS) procedure, but is based on mode of action or alternatively if there is insufficient data to support a nonlinear mode of action. In brief, it involves drawing a straight line from the point of departure (LED_{10}) to the origin (i.e., zero). When there is no evidence of linearity or there is a nonlinear mode of action, the default approach is the margin of exposure (MOE) analysis. The MOE approach computes the ratio between the LED_{10} and the environmental exposure, and the analysis begins from the point of departure that is adjusted for toxicokinetic differences between species to give a human equivalent dose.

Finally it should be noted that prior to the FQPA in 1996, the Delaney clause prohibited the establishment of tolerances or maximum allowable levels for food additives if it has been shown to induce cancer in human or animal. This is an important change in regulations because pesticide residues were considered as food additives. Because of the FQPA, pesticide residues are no longer regarded as food additives, and there is no prohibition against setting tolerances for carcinogens.

24.5 PBPK MODELING

Physiologically based pharmacokinetic (PBPK) modeling has been used in risk assessment to make more scientifically based extrapolations, and at the same time to help explore and reduce inherent uncertainties. Historically pharmacokinetics has relied on empirical models, and in many instances this process offers little insight into mechanisms of absorption, distribution, and clearance of hazardous agents and does not facilitate translation from animal experiments to human exposures. For example, dose scaling using by body weight or size may often time overestimate or underestimate toxicant levels at the target tissue. PBPK models can help predict tissue concentrations in different species under various conditions based on *independent* anatomical, physiological, and biochemical parameters. In these analyzes physiological parameters such as organ volumes, tissue-blood partition coefficients, and blood flow to specific tissue compartments described by the model, are calculated or obtained from the literature and integrated into the model. Monte Carlo analysis, a form of uncertainty analysis, can now be performed, and this allows for the propagation of uncertainty through a model that results in estimation of the variance of model output. This can be achieved by randomly sampling model parameters from defined distributions; some parameters such as cardiac output, metabolic, and log P parameters, may have a lognormal distribution, while other parameters may be normal or uniform. In essence, the Monte Carlo analysis when coupled with PBPK characterizes the distribution of potential risk

in a population by using a *range* of potential values for each input parameter (not single values) as well as an estimate of how these values are distributed (Clewell and Andersen, 1996). By these approaches, uncertainty is identifiable and quantifiable, and can reduce inappropriate levels of concern in reporting the risk of chemical exposure. These mathematical modeling approaches also help identify areas of potential scientific research that could improve the human health assessment.

In recent years there have been significant efforts at harmonizating noncancer and cancer risk assessments (Barton et al., 1998; Clewell et al., 2002), and in this respect PKPD modeling can be a very useful tool in the risk assessment process. For example, recall that noncancer risk assessment addresses variability in a population by dividing the NOAEL by 10, whereas the cancer risk assessment does not address this quantitatively. PBPK modeling coupled with Monte Carlo analysis is one approach as described in the previous paragraph that will help address this level of uncertainty in the risk assessment. In conclusion, it should be noted that PBPK modeling has been utilized with very few toxicants. It is hoped that risk assessment policy will encourage the use of this tool as well as other appropriate models to integrate mechanistic information and the pharmacokinetics (dosimetry), and pharmacodynamics (dose response) of toxicants. Improved quantitative risk assessments will ultimately provide scientifically sound information that will influence the risk management decision process.

SUGGESTED READING

ATSDR. *Guidance for the Preparation of Toxicological Profiles*. ATSDR, US Public Health Service. 1993.

Battelle. Subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Report to US Department of Health and Human Services, National Toxicology Program, Research Triangle Park, NC, by Battelle Columbus Laboratories, Columbus, OH, 1980.

Borton, H. A., M. E. Anderson, and H. J. Clewell. Harmonization: Developing consistent guidelines for applying mode of action and dosimetry information for applying mode of action and dosimetry information to cancer and noncancer risk assessment. *Hum. Ecol. Risk Assess.* **4**: 75–115, 1998.

Clewell, H. J., and M. E. Andersen. Use of physiologically based pharmacokinetic modeling to investigate individual versus population risk. *Toxicol.* **111**(1–3): 315–329, 1996.

Clewell, H. J., M. E. Andersen, and H. A. Barton. A consistent approach for the application of pharmacokinetic modeling in cancer and noncancer risk assessment. *Envion. Health. Perspect.* **110**: 85–93, 2002.

Conolly, R. B., and B. E. Butterworth. Biologically based dose response model for hepatic toxicity: a mechanistically based replacment for traditional estimates of noncancer risk. *Toxicol. Lett.* **82–83**: 901–906, 1995.

Conolly, R. B., B. D. Beck, and J. I. Goodman. Stimulating research to improve the scientific basis of risk assessment. *Toxicol. Sci.* **49**: 1–4, 1999.

Crump, K. S. A new method for determining allowable daily intakes. *Fundam. Appl. Toxicol.* **4**: 854–871, 1984.

EPA. Guidelines for Carcinogen Risk Assessment. *Fed. Reg.* **51**: 33992–34003, 1986.

EPA. Proposed Guidelines for Carcinogen Risk Assessment. *Fed. Reg.* **61**: 17960–18011, 1996.

EPA. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, US Environmental Protection Agency, NCEA-F-0644, July 1999, Review Draft.

EPA. *Risk Assessment Guidance for Superfund*, Vol. 1. *Human Health Evaluation Manual* (Part A). US EPA. 1989.

Haddad, S., M. Beliveau, R. Tardif, and K. Krishnan. A PBPK modeling-based approach to account for interactions in the health risk assessment of chemical mixtures. *Toxicol. Sci.* **63**: 125–131, 2001.

Jarabek, A. M., The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches. *Toxicol. Lett.* **79**(1–3): 171–184, 1995.

Krishnan, K., H. J. Clewell, and M. E. Andersen Physiologically based pharmacokinetic analyzes of simple mixtures. *Environ. Health Perspec.* **102** (supp. 9): 151–155, 1994.

NTP. National Toxicology Program. Technical report series No. 410. Toxicology and carcinogenesis studies of naphthalene (CAS No. 91-20-3) in B6C3F1 mice (inhalation studies). Research Triangle Park, NC. US Department of Health and Human Services, Public Health Services, National Institutes of Health. NIH Publication No. 92–3141, 1992.

Page, N. P., D. V Singh, W. Farland, J. I. Goodman, R. B. Conolly, M. E Andersen, H. J. Clewell, C. B. Frederick, H. Yamasaki, G. Lucier. Implementation of EPA Revised Cancer Assessment Guidelines: Incorporation of Mechanistic and Pharmacokinetic Data. *Fundam. Appl. Toxicol.* **37**: 16–36, 1997.

Scheuplein, R. J. Pesticides and infant risk: Is there a need for an additional safety margin? *Regul. Toxicol. Pharmacol.* **31**(3): 267–279, 2000.

Environmental Risk Assessment

DAMIAN SHEA

28.1 INTRODUCTION

Risk assessment is the process of assigning magnitudes and probabilities to adverse effects associated with an event. The development of risk assessment methodology has focused on accidental events (e.g., an airplane crash) and specific environmental stresses to humans (exposure of humans to chemicals), and thus most risk assessment is characterized by discrete events or stresses affecting well-defined endpoints (e.g., incidence of human death or cancer). This *single stress–single end point* relationship allows the use of relatively simple statistical and mechanistic models to estimate risk and is widely used in human health risk assessment. However, this simple paradigm has only partial applicability to ecological risk assessment because of the inherent complexity of ecological systems and the exposure to numerous physical, chemical, and biological stresses that have both direct and indirect effects on a diversity of ecological components, processes, and endpoints. Thus, although the roots of ecological risk assessment can be found in human health risk assessment, the methodology for ecological risk assessment is not well developed and the estimated risks are highly uncertain. Despite these limitations, resource managers and regulators are looking to ecological risk assessment to provide a scientific basis for prioritizing problems that pose the greatest ecological risk and to focus research efforts in areas that will yield the greatest reduction in uncertainty.

To this end the US Environmental Protection Agency has issued guidelines for planning and conducting ecological risk assessments. Because of the complexity and uncertainty associated with ecological risk assessment the EPA guidelines provide only a loose framework for organizing and analyzing data, information, assumptions, and uncertainties to evaluate the likelihood of adverse ecological effects. However, the guidelines represent a broad consensus of the present scientific knowledge and experience on ecological risk assessment. This chapter presents a brief overview of the ecological risk assessment process as presently described by the EPA.

Ecological risk assessment can be defined as:

> The process that evaluates the likelihood that adverse ecological effects may occur or are occurring as a result of exposure to one or more stressors.

A Textbook of Modern Toxicology, Third Edition, edited by Ernest Hodgson
ISBN 0-471-26508-X

Estimating the *likelihood* can range from qualitative judgments to quantitative probabilities, though quantitative risk estimates still are rare in ecological risk assessment. The *adverse ecological effects* are changes that are considered undesirable because they alter valued structural or functional characteristics of ecological systems and usually include the type, intensity, and scale of the effect as well as the potential for recovery. The statement that effects *may occur or are occurring* refers to the dual *prospective* and *retrospective* nature of ecological risk assessment. The inclusion of *one or more stressors* is a recognition that ecological risk assessments may address single or multiple chemical, physical, and/or biological stressors. Because risk assessments are conducted to provide input to management decisions, most risk assessments focus on stressors generated or influenced by anthropogenic activity. However, natural phenomena also will induce stress that results in adverse ecological effects and cannot be ignored.

The overall ecological risk assessment process is shown in Figure 28.1 and includes three primary phases: (1) problem formulation, (2) analysis, and (3) risk characterization. Problem formulation includes the development of a conceptual model

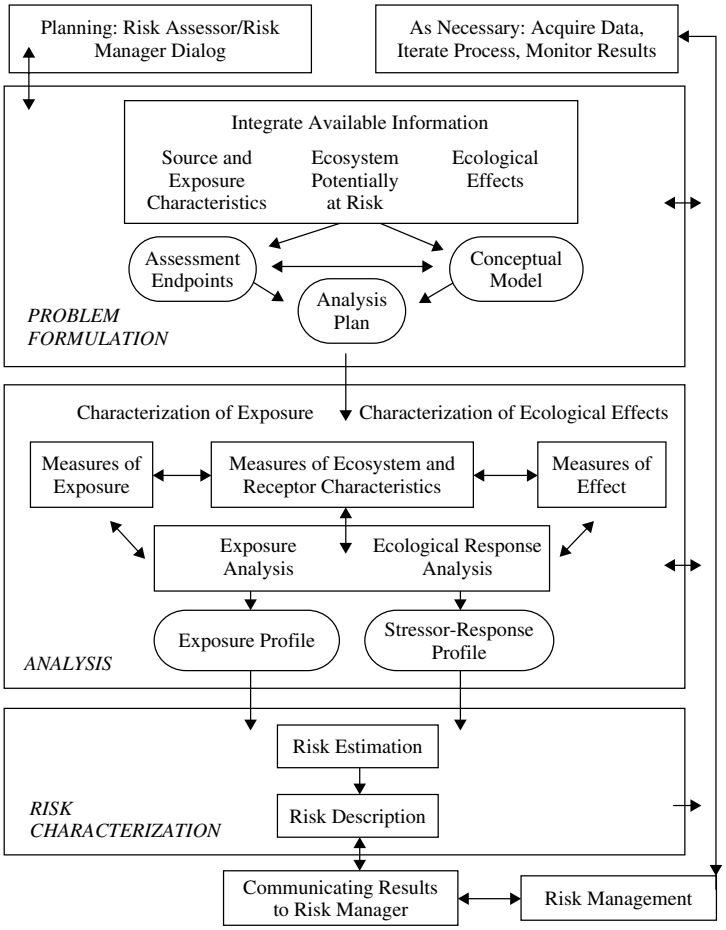

Figure 28.1 The ecological risk assessment framework as set forth by the US Environmental Protection Agency.

of stressor-ecosystem interactions and the identification of risk assessment end points. The analysis phase involves evaluating exposure to stressors and the relationship between stressor characteristics and ecological effects. Risk characterization includes estimating risk through integration of exposure and stressor-response profiles, describing risk by establishing lines of evidence and determining ecological effects, and communicating this description to risk managers. While discussions between risk assessors and risk managers are emphasized both at risk assessment initiation (planning) and completion (communicating results), usually a clear distinction is drawn between risk assessment and risk management. Risk assessment focuses on scientifically evaluating the likelihood of adverse effects, and risk management involves the selection of a course of action in response to an identified risk that is based on many factors (e.g., social, legal, or economic) in addition to the risk assessment results. Monitoring and other data acquisition is often necessary during any phase of the risk assessment process and the entire process is typically iterative rather than linear. The evaluation of new data or information may require revisiting a part of the process or conducting a new assessment.

28.2 FORMULATING THE PROBLEM

Problem formulation is a process for generating and evaluating preliminary hypotheses about why ecological effects have occurred, or may occur, because of human activities. During problem formulation, management goals are evaluated to help establish objectives for the risk assessment, the ecological problem is defined, and the plan for analyzing data and characterizing risk is developed. The objective of this process is to develop (1) assessment end points that adequately reflect management goals and the ecosystem they represent and (2) conceptual models that describe critical relationships between a stressor and assessment end point or among several stressors and assessment end points. The assessment end points and the conceptual models are then integrated to develop a plan or proposal for risk analysis.

28.2.1 Selecting Assessment End Points

Assessment end points are *explicit expressions of the actual environmental value that is to be protected* and they link the risk assessment to management concerns. Assessment end points include both a valued or key ecological entity and an attribute of that entity that is important to protect and that is potentially at risk. The scientific basis for a risk assessment is enhanced when assessment end points are both ecologically relevant and susceptible to the stressors of concern. Assessment endpoints that also logically represent societal values and management goals will increase the likelihood that the risk assessment will be understood and used in management decisions.

Ecological Relevance. Ecologically relevant end points reflect important attributes of the ecosystem and can be functionally related to other components of the ecosystem; they help sustain the structure, function, and biodiversity of an ecosystem. For example, ecologically relevant end points might contribute to the food base (e.g., primary production), provide habitat, promote regeneration of critical resources (e.g.,

nutrient cycling), or reflect the structure of the community, ecosystem, or landscape (e.g., species diversity). Ecological relevance becomes most useful when it is possible to identify the potential cascade of adverse effects that could result from a critical initiating effect such as a change in ecosystem function. The selection of assessment end points that address both specific organisms of concern and landscape-level ecosystem processes becomes increasingly important (and more difficult) in landscape-level risk assessments. In these cases it may be possible to select one or more species and an ecosystem process to represent larger functional community or ecosystem processes. Extrapolations like these must be explicitly described in the conceptual model (see Section 28.2.2).

Susceptibility to Stressors. Ecological resources or entities are considered susceptible if they are sensitive to a human-induced stressor to which they are exposed. *Sensitivity* represents how readily an ecological entity responds to a particular stressor. Measures of sensitivity may include mortality or decreased growth or fecundity resulting from exposure to a toxicant, behavioral abnormalities such as avoidance of food-source areas or nesting sites because of the proximity of stressors such as noise or habitat alteration. Sensitivity is directly related to the mode of action of the stressors. For example, chemical sensitivity is influenced by individual physiology, genetics, and metabolism. Sensitivity also is influenced by individual and community life-history characteristics. For example, species with long life cycles and low reproductive rates will be more vulnerable to extinction from increases in mortality than those with short life cycles and high reproductive rates. Species with large home ranges may be more sensitive to habitat fragmentation compared to those species with smaller home ranges within a fragment. Sensitivity may be related to the life stage of an organism when exposed to a stressor. Young animals often are more sensitive to stressors than adults. In addition events like migration and molting often increase sensitivity because they require significant energy expenditure that make these organisms more vulnerable to stressors. Sensitivity also may be increased by the presence of other stressors or natural disturbances.

Exposure is the other key determinant in susceptibility. In ecological terms, exposure can mean co-occurrence, contact, or the absence of contact, depending on the stressor and assessment end point. The characteristics and conditions of exposure will influence how an ecological entity responds to a stressor and thus determine what ecological entities might be susceptible. Therefore one must consider information on the proximity of an ecological entity to the stressor along with the timing (e.g., frequency and duration relative to sensitive life stages) and intensity of exposure. Note that adverse effects may be observed even at very low stressor exposures if a necessary resource is limited during a critical life stage. For example, if fish are unable to find suitable nesting sites during their reproductive phase, risk is significant even when water quality is high and food sources are abundant.

Exposure may take place at one point in space and time, but effects may not arise until another place or time. Both life history characteristics and the circumstances of exposure influence susceptibility in this case. For example, exposure of a population to endocrine-modulating chemicals can affect the sex ratio of offspring, but the population impacts of this exposure may not become apparent until years later when the cohort of affected animals begins to reproduce. Delayed effects and multiple stressor exposures add complexity to evaluations of susceptibility. For example, although toxicity

tests may determine receptor sensitivity to one stressor, the degree of susceptibility may depend on the co-occurrence of another stressor that significantly alters receptor response. Again, conceptual models need to reflect these additional factors.

Defining Assessment End Points. Assessment end points provide a transition between management goals and the specific measures used in an assessment by helping identify measurable attributes to quantify and model. However, in contrast to management goals, no intrinsic value is assigned to the end point, so it does not contain words such as *protect* or *maintain* and it does not indicate a desirable direction for change. Two aspects are required to define an assessment end point. The first is the valued ecological entity such as a species, a functional group of species, an ecosystem function or characteristic, or a specific valued habitat. The second is the characteristic about the entity of concern that is important to protect and potentially at risk.

Expert judgment and an understanding of the characteristics and function of an ecosystem are important for translating general goals into usable assessment end points. End points that are too broad and vague (ecological health) cannot be linked to specific measurements. End points that are too narrowly defined (hatching success of bald eagles) may overlook important characteristics of the ecosystem and fail to include critical variables. Clearly defined assessment end points provide both direction and boundaries for the risk assessment.

Assessment end points directly influence the type, characteristics, and interpretation of data and information used for analysis and the scale and character of the assessment. For example, an assessment end point such as "fecundity of bivalves" defines local population characteristics and requires very different types of data and ecosystem characterization compared with "aquatic community structure and function." When concerns are on a local scale, the assessment end points should not focus on landscape concerns. But if ecosystem processes and landscape patterns are being considered, survival of a single species would provide inadequate representation of this larger scale.

The presence of multiple stressors also influences the selection of assessment end points. When it is possible to select one assessment end point that is sensitive to many of the identified stressors, yet responds in different ways to different stressors, it is possible to consider the combined effects of multiple stressors while still discriminating among effects. For example, if recruitment of a fish population is the assessment end point, it is important to recognize that recruitment may be adversely affected at several life stages, in different habitats, through different ways, by different stressors. The measures of effect, exposure, and ecosystem and receptor characteristics chosen to evaluate recruitment provide a basis for discriminating among different stressors, individual effects, and their combined effect.

Although many potential assessment end points may be identified, practical considerations often drive their selection. For example, assessment end points usually must reflect environmental values that are protected by law or that environmental managers and the general public recognize as a critical resource or an ecological function that would be significantly impaired if the resource were altered. Another example of a practical consideration is the extrapolation across scales of time, space, or level of biological organization. When the attributes of an assessment end point can be measured directly, extrapolation is unnecessary and this uncertainty is avoided. Assessment end points that cannot be linked with measurable attributes are not appropriate for a risk

assessment. However, assessment end points that cannot be measured directly but can be represented by surrogate measures that are easily monitored and modeled can still provide a good foundation for the risk assessment.

28.2.2 Developing Conceptual Models

Conceptual models link anthropogenic activities with stressors and evaluate the relationships among exposure pathways, ecological effects, and ecological receptors. The models also may describe natural processes that influence these relationships. Conceptual models include a set of risk hypotheses that describe predicted relationships between stressor, exposure, and assessment end point response, along with the rationale for their selection. Risk hypotheses are hypotheses in the broad scientific sense; they do not necessarily involve statistical testing of null and alternative hypotheses or any particular analytical approach. Risk hypotheses may predict the effects of a stressor, or they may postulate what stressors may have caused observed ecological effects.

Diagrams can be used to illustrate the relationships described by the conceptual model and risk hypotheses. Conceptual model diagrams are useful tools for communicating important pathways and for identifying major sources of uncertainty. These diagrams and risk hypotheses can be used to identify the most important pathways and relationships to consider in the analysis phase. The hypotheses considered most likely to contribute to risk are identified for subsequent evaluation in the risk assessment.

The complexity of the conceptual model depends on the complexity of the problem, number of stressors and assessment end points being considered, nature of effects, and characteristics of the ecosystem. For single stressors and single assessment end points, conceptual models can be relatively simple relationships. In cases where conceptual models describe, besides the pathways of individual stressors and assessment end points, the interaction of multiple and diverse stressors and assessment end points, several submodels would be required to describe individual pathways. Other models may then be used to explore how these individual pathways interact. An example of a conceptual model for a watershed in shown in Figure 28.2.

28.2.3 Selecting Measures

The last step in the problem formulation phase is the development of an analysis plan or proposal that identifies measures to evaluate each risk hypothesis and that describes the assessment design, data needs, assumptions, extrapolations, and specific methods for conducting the analysis. There are three categories of measures that can be selected. *Measures of effect* (also called *measurement end points*) are measures used to evaluate the response of the assessment end point when exposed to a stressor. *Measures of exposure* are measures of how exposure may be occurring, including how a stressor moves through the environment and how it may co-occur with the assessment end point. *Measures of ecosystem and receptor characteristics* include ecosystem characteristics that influence the behavior and location of assessment end points, the distribution of a stressor, and life history characteristics of the assessment end point that may affect exposure or response to the stressor. These diverse measures increase in importance as the complexity of the assessment increases.

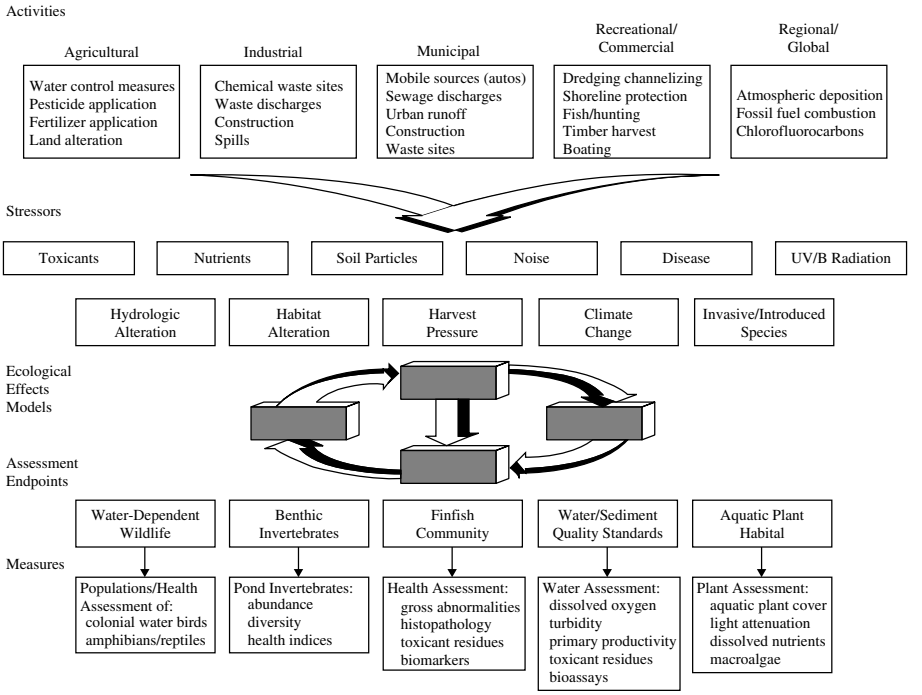

Figure 28.2 An example of a conceptual model for a watershed. Human activities, shown at the top of the diagram, result in various stressors that induce ecological effects. Assessment end points and related measures that are associated with these effects are shown at the bottom of the diagram.

An important consideration in the identification of these measures is their response sensitivity and ecosystem relevance. Response sensitivity is usually highest with measures at the lower levels of biological organization, but the ecosystem relevance is highest at the higher levels of biological organization. This dichotomy is illustrated in Figure 28.3. In general, the time required to illicit a response also increases with the level of biological organization. Note that toxicologists focus on measures at lower levels of biological organization, relying on an extrapolation of the toxicant effects on populations and communities that are initiated at the molecular/cellular level and, if this insult is not corrected for, or adapted to, then effects on physiological systems and individual organisms. For certain toxic modes of action (e.g., reproductive toxicity), this could result in effects at the population and community levels. In contrast, ecologists focus on measures at the population level or higher for obvious reasons of ecological relevance. A combination of measures often is necessary to provide reasonable sensitivity, ecosystem relevance, and causal relationships.

28.3 ANALYZING EXPOSURE AND EFFECTS INFORMATION

The second phase of ecological risk assessment, the analysis phase, includes two principal activities: characterization of exposure and characterization of ecological effects (Figure 28.1).

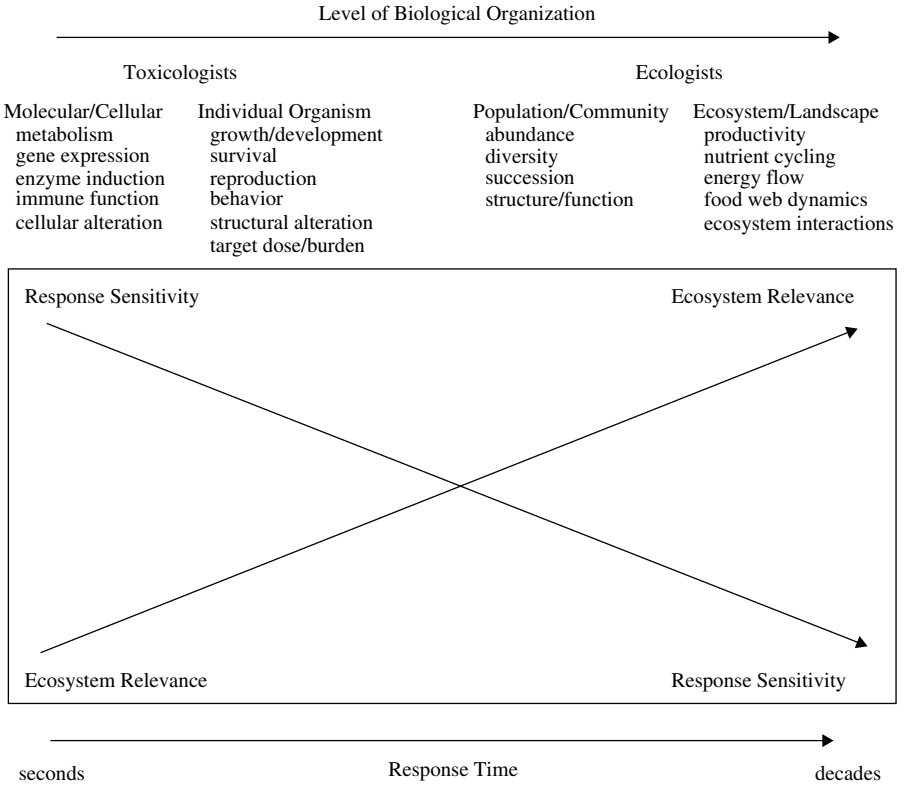

Figure 28.3 The response time and sensitivity of an ecological receptor is a function of the level of biological organization. Higher levels of organization have greater ecosystem relevance. However, as the level of biological organization increases, response time increases, sensitivity decreases, and causal relationships become more uncertain. Ecological risk assessments must balance the need for sensitive, timely, and well-established responses with ecological relevance.

28.3.1 Characterizing Exposure

In exposure characterization, credible and relevant data are analyzed to describe the source(s) of stressors, the distribution of stressors in the environment, and the contact or co-occurrence of stressors with ecological receptors. An exposure profile is developed that identifies receptors and exposure pathways, describes the intensity and spatial and temporal extent of exposure, describes the impact of variability and uncertainty on exposure estimates, and presents a conclusion about the likelihood that exposure will occur.

A source description identifies where the stressor originates, describes what stressors are generated, and considers other sources of the stressor. Exposure analysis may start with the source when it is known, but some analyses may begin with known exposures and attempt to link them to sources, while other analyses may start with known stressors and attempt to identify sources and quantify contact or co-occurrence. The source description includes what is known about the intensity, timing, and location of the stressor and whether other constituents emitted by the source influence transport, transformation, or bioavailability of the stressor of interest.

Many stressors have natural counterparts and/or multiple sources that must be considered. For example, many chemicals occur naturally (e.g., most metals), are generally widespread due to multiple sources (e.g., polycyclic aromatic hydrocarbons), or may have significant sources outside the boundaries of the current assessment (e.g., regional atmospheric deposition of PCBs). Many physical stressors also have natural counterparts such as sedimentation from construction activities versus natural erosion. In addition human activities may change the magnitude or frequency of natural disturbance cycles such as the frequency and severity of flooding. Source characterization can be particularly important for new biological stressors (e.g., invasive species), since many of the strategies for reducing risks focus on preventing entry in the first place. Once the source is identified, the likelihood of entry may be characterized qualitatively.

Because exposure occurs where receptors co-occur with or contact stressors in the environment, characterizing the spatial and temporal distribution of a stressor is a necessary precursor to estimating exposure. The stressor's spatial and temporal distribution in the environment is described by evaluating the pathways that stressors take from the source as well as the formation and subsequent distribution of secondary stressors. For chemical stressors, the evaluation of pathways usually follows the type of transport and fate modeling described in Chapter 27. Some physical stressors such as sedimentation also can be modeled, but other physical stressors require no modeling because they eliminate entire ecosystems or portions of them, such as when a wetland is filled, a resource is harvested, or an area is flooded.

The movement of biological stressors have been described as diffusion and/or jump-dispersal processes. Diffusion involves a gradual spread from the site of introduction and is a function primarily of reproductive rates and motility. Jump-dispersal involves erratic spreads over periods of time, usually by means of a vector. The gypsy moth and zebra mussel have spread this way; the gypsy moth via egg masses on vehicles and the zebra mussel via boat ballast water. Biological stressors can use both diffusion and jump-dispersal strategies, which makes it difficult to predict dispersal rates. An additional complication is that biological stressors are influenced by their own survival and reproduction.

The creation of secondary stressors can greatly alter risk. Secondary stressors can be formed through biotic or abiotic transformation processes and may be of greater or lesser concern than the primary stressor. Physical disturbances can generate secondary stressors, such as when the removal of riparian vegetation results in increased nutrients, sedimentation, and altered stream flow. For chemicals, the evaluation of secondary stressors usually focuses on metabolites or degradation products. In addition secondary stressors can be formed through ecosystem processes. For example, nutrient inputs into an estuary can decrease dissolved oxygen concentrations because they increase primary production and subsequent decomposition. A changeover from an aerobic to an anaerobic environment often is accompanied by the production of sulfide via sulfate-reducing bacteria. Sulfide can act as a secondary stressor to oxygen-dependent organisms, but it also can reduce exposure to metals through the precipitation of metal sulfides (see Chapter 27).

The distribution of stressors in the environment can be described using measurements, models, or a combination of the two. If stressors have already been released, direct measurements of environmental media or a combination of modeling and measurement is preferred. However, a modeling approach may be necessary if the assessment is intended to predict future scenarios or if measurements are not possible or practicable.

28.3.2 Characterizing Ecological Effects

In ecological effects characterization, relevant data are analyzed to evaluate stressor-response relationships and/or to provide evidence that exposure to a stressor causes an observed response. The characterization describes the effects that are elicited by a stressor, links these effects with the assessment endpoints, and evaluates how the effects change with varying stressor levels. The conclusions of the ecological effects characterization are summarized in a stressor-response profile.

Analyzing Ecological Response. Ecological response analysis has three primary components: determining the relationship between stressor exposure and ecological effects, evaluating the plausibility that effects may occur or are occurring as a result of the exposure, and linking measurable ecological effects with the assessment end points.

Evaluating ecological risks requires an understanding of the relationships between stressor exposure and resulting ecological responses. The stressor-response relationships used in a particular assessment depend on the scope and nature of the ecological risk assessment as defined in problem formulation and reflected in the analysis plan. For example, a point estimate of an effect (e.g., an LC50) might be compared with point estimates from other stressors. The stressor-response function (e.g., shape of the curve) may be critical for determining the presence or absence of an effects threshold or for evaluating incremental risks, or stressor-response functions may be used as input for ecological effects models. If sufficient data are available, cumulative distribution functions can be constructed using multiple point estimates of effects. Process models that already incorporate empirically derived stressor-response functions also can be used. However, many stressor-response relationships are very complex, and ecological systems frequently show responses to stressors that involve abrupt shifts to new community or system types.

In simple cases the response will be one variable (e.g., mortality) and quantitative univariate analysis can be used. If the response of interest is composed of many individual variables (e.g., species abundances in an aquatic community), multivariate statistical techniques must be used. Multivariate techniques (e.g., factor and cluster analysis) have a long history of use in ecology but have not yet been extensively applied in risk assessment. Stressor-response relationships can be described using any of the dimensions of exposure (i.e., intensity, time, space). Intensity is probably the most familiar dimension and is often used for chemicals (e.g., dose, concentration). The duration of exposure also can be used for chemical stressor-response relationships; for example, median acute effects levels are always associated with a time parameter (e.g., 24 h, 48 h, 96 h). Both the time and spatial dimensions of exposure can be important for physical disturbances such as flooding. Single-point estimates and stressor-response curves can be generated for some biological stressors. For pathogens such as bacteria and fungi, inoculum levels may be related to the level of symptoms in a host or actual signs of the pathogen. For other biological stressors such as introduced species, developing simple stressor-response relationships may be inappropriate.

Causality is the relationship between cause (one or more stressors) and effect (assessment end point response to one or more stressors). Without a sound basis for linking cause and effect, uncertainty in the conclusions of an ecological risk assessment will be high. Developing causal relationships is especially important for risk assessments driven by observed adverse ecological effects such as fish kills or long-term declines

in a population. Criteria need to be established for evaluating causality. For chemicals, ecotoxicologists have slightly modified Koch's postulates to provide evidence of causality:

1. The injury, dysfunction, or other putative effect of the toxicant must be regularly associated with exposure to the toxicant and any contributory causal factors.
2. Indicators of exposure to the toxicant must be found in the affected organisms.
3. The toxic effects must be seen when normal organisms or communities are exposed to the toxicant under controlled conditions, and any contributory factors should be manifested in the same way during controlled exposures.
4. The same indicators of exposure and effects must be identified in the controlled exposures as in the field.

While useful as an ideal, this approach may not be practical if resources for experimentation are not available or if an adverse effect may be occurring over such a wide spatial extent that experimentation and correlation may prove difficult or yield equivocal results. In most cases extrapolation will be necessary to evaluate causality. The scope of the risk assessment also influences extrapolation through the nature of the assessment end point. Preliminary assessments that evaluate risks to general trophic levels, such as fish and birds, may extrapolate among different genera or families to obtain a range of sensitivity to the stressor. On the other hand, assessments concerned with management strategies for a particular species may employ population models.

Whatever methods are employed to link assessment end points with measures of effect, it is important to apply the methods in a manner consistent with sound ecological and toxicological principles. For example, it is inappropriate to use structure-activity relationships to predict toxicity from chemical structure unless the chemical under consideration has a similar mode of toxic action to the reference chemicals. Similarly extrapolations from upland avian species to waterfowl may be more credible if factors such as differences in food preferences, physiology, and seasonal behavior (e.g., mating and migration habits) are considered.

Finally, many extrapolation methods are limited by the availability of suitable databases. Although these databases are generally largest for chemical stressors and aquatic species, even in these cases data do not exist for all taxa or effects. Chemical effects databases for mammals, amphibians, or reptiles are extremely limited, and there is even less information on most biological and physical stressors. Extrapolations and models are only as useful as the data on which they are based and should recognize the great uncertainties associated with extrapolations that lack an adequate empirical or process-based rationale.

Developing a Stressor-Response Profile. The final activity of the ecological response analysis is developing a stressor-response profile to evaluate single species, populations, general trophic levels, communities, ecosystems, or landscapes—whatever is appropriate for the defined assessment end points. For example, if a single species is affected, effects should represent appropriate parameters such as effects on mortality, growth, and reproduction, while at the community level, effects may be summarized in terms of structure or function depending on the assessment end point. At the landscape level, there may be a suite of assessment end points, and each should be addressed separately. The stressor-response profile summarizes the nature and intensity of effect(s),

the time scale for recovery (where appropriate), causal information linking the stressor with observed effects, and uncertainties associated with the analysis.

28.4 CHARACTERIZING RISK

Risk characterization is the final phase of an ecological risk assessment (Figure 28.1). During risk characterization, risks are estimated and interpreted and the strengths, limitations, assumptions, and major uncertainties are summarized. Risks are estimated by integrating exposure and stressor-response profiles using a wide range of techniques such as comparisons of point estimates or distributions of exposure and effects data, process models, or empirical approaches such as field observational data. Risks are described by evaluating the evidence supporting or refuting the risk estimate(s) and interpreting the adverse effects on the assessment end point. Criteria for evaluating adversity include the nature and intensity of effects, spatial and temporal scales, and the potential for recovery. Agreement among different lines of evidence of risk increases confidence in the conclusions of a risk assessment.

28.4.1 Estimating Risk

Risk estimation determines the likelihood of adverse effects to assessment end points by integrating exposure and effects data and evaluating any associated uncertainties. The process uses the exposure and stressor-response profiles. Risks can be estimated by one or more of the following approaches: (1) estimates based on best professional judgment and expressed as qualitative categories such as low, medium, or high; (2) estimates comparing single-point estimates of exposure and effects such as a simple ratio of exposure concentration to effects concentration (quotient method); (3) estimates incorporating the entire stressor-response relationship often as a nonlinear function of exposure; (4) estimates incorporating variability in exposure and effects estimates providing the capability to predict changes in the magnitude and likelihood of effects at different exposure scenarios; (5) estimates based on process models that rely partially or entirely on theoretical approximations of exposure and effects; and (6) estimates based on empirical approaches, including field observational data. An example of the first approach, using qualitative categorization, is shown in Figure 28.4.

28.4.2 Describing Risk

After risks have been estimated, available information must be integrated and interpreted to form conclusions about risks to the assessment endpoints. Risk descriptions include an evaluation of the lines of evidence supporting or refuting the risk estimate(s) and an interpretation of the adverse effects on the assessment end point. Confidence in the conclusions of a risk assessment may be increased by using several lines of evidence to interpret and compare risk estimates. These lines of evidence may be derived from different sources or by different techniques relevant to adverse effects on the assessment end points, such as quotient estimates, modeling results, field experiments,

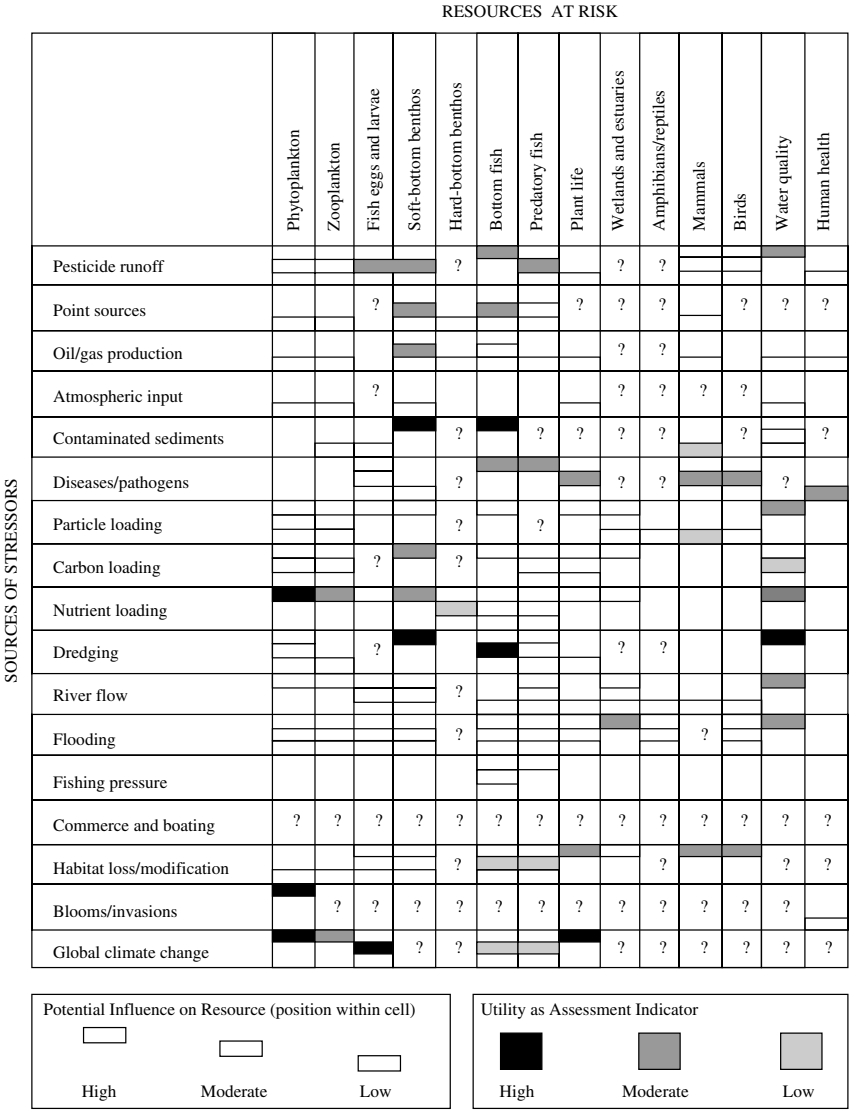

Figure 28.4 An example of a qualitative categorization of ecological risk for a hypothetical matrix of stressors and resources at risk.

or field observations. Some of the factors to consider when evaluating separate lines of evidence are:

- Relevance of evidence to the assessment end points.
- Relevance of evidence to the conceptual model.
- Sufficiency and quality of data and experimental designs used in supporting studies.
- Strength of cause/effect relationships.
- Relative uncertainties of each line of evidence and their direction.

At this point in risk characterization, the changes expected in the assessment end points have been estimated and described. The next step is to interpret whether these changes are considered adverse and meaningful. Meaningful adverse changes are defined by ecological and/or social concerns, and thus usually depend on the best professional judgment of the risk assessor. Five criteria have been proposed by EPA for evaluating adverse changes in assessment end points:

1. Nature of effects
2. Intensity of effects
3. Spatial scale
4. Temporal scale
5. Potential for recovery

The extent to which the five criteria are evaluated depends on the scope and complexity of the ecological risk assessment. However, understanding the underlying assumptions and science policy judgments is important even in simple cases. For example, when exceedence of a previously established decision rule such as a benchmark stressor level or water quality criterion is used as evidence of adversity, the reasons why exceedences of the benchmark are considered adverse should be clearly understood.

To distinguish ecological changes that are adverse from those ecological events that are within the normal pattern of ecosystem variability or result in little or no meaningful alteration of biota, it is important to consider the nature and intensity of effects. For example, an assessment end point involving survival, growth, and reproduction of a species must consider whether predicted effects involve survival and reproduction or only growth. Or if survival of offspring are affected, the relative loss must be considered.

It is important to consider both the ecological and statistical contexts of an effect when evaluating intensity. For example, a statistically significant 1% decrease in fish growth may not be relevant to an assessment end point of fish population viability, and a 10% decline in reproduction may be worse for a population of slowly reproducing marine mammals than for rapidly reproducing planktonic algae.

Natural ecosystem variation can make it very difficult to observe (detect) stressor-related perturbations. For example, natural fluctuations in marine fish populations are often very large and cyclic events (e.g., fish migration) are very important in natural systems. Predicting the effects of anthropogenic stressors against this background of variation can be very difficult. Thus a lack of statistically significant effects in a field study does not automatically mean that adverse ecological effects are absent. Rather, factors such as statistical power to detect differences, natural variability, and other lines of evidence must be considered in reaching conclusions about risk.

Spatial and temporal scales also need to be considered in assessing the adversity of the effects. The spatial dimension encompasses both the extent and pattern of effect as well as the context of the effect within the landscape. Factors to consider include the absolute area affected, the extent of critical habitats affected compared with a larger area of interest, and the role or use of the affected area within the landscape. Adverse effects to assessment end points vary with the absolute area of the effect. A larger affected area may be (1) subject to a greater number of other stressors, increasing the complications from stressor interactions; (2) more likely to contain sensitive species or

habitats; or (3) more susceptible to landscape-level changes because many ecosystems may be altered by the stressors.

Nevertheless, a smaller area of effect is not always associated with lower risk. The function of an area within the landscape may be more important than the absolute area. Destruction of small but unique areas, such as submerged vegetation at the land-water margin, may have important effects on local wildlife populations. Also, in river systems, both riffle and pool areas provide important microhabitats that maintain the structure and function of the total river ecosystem. Stressors acting on some of these microhabitats may present a significant risk to the entire system. Spatial factors also are important for many species because of the linkages between ecological landscapes and population dynamics. Linkages between one or more landscapes can provide refuge for affected populations, and species may require adequate corridors between habitat patches for successful migration.

The temporal scale for ecosystems can vary from seconds (photosynthesis, prokaryotic reproduction) to centuries (global climate change). Changes within a forest ecosystem can occur gradually over decades or centuries and may be affected by slowly changing external factors such as climate. The time scale of stressor-induced changes operates within the context of multiple natural time scales. In addition temporal responses for ecosystems may involve intrinsic time lags, so responses from a stressor may be delayed. Thus it is important to distinguish the long-term impacts of a stressor from the immediately visible effects. For example, visible changes resulting from eutrophication of aquatic systems (turbidity, excessive macrophyte growth, population decline) may not become evident for many years after initial increases in nutrient levels.

From the temporal scale of adverse effects we come to a consideration of recovery. Recovery is the rate and extent of return of a population or community to a condition that existed before the introduction of a stressor. Because ecosystems are dynamic and even under natural conditions are constantly changing in response to changes in the physical environment (weather, natural catastrophes, etc.) or other factors, it is unrealistic to expect that a system will remain static at some level or return to exactly the same state that it was before it was disturbed. Thus the attributes of a "recovered" system must be carefully defined. Examples might include productivity declines in an eutrophic system, re-establishment of a species at a particular density, species re-colonization of a damaged habitat, or the restoration of health of diseased organisms.

Recovery can be evaluated despite the difficulty in predicting events in ecological systems. For example, it is possible to distinguish changes that are usually reversible (e.g., recovery of a stream from sewage effluent discharge), frequently irreversible (e.g., establishment of introduced species), and always irreversible (e.g., species extinction). It is important to consider whether significant structural or functional changes have occurred in a system that might render changes irreversible. For example, physical alterations such as deforestation can change soil structure and seed sources such that forests cannot easily grow again.

Natural disturbance patterns can be very important when evaluating the likelihood of recovery from anthropogenic stressors. Ecosystems that have been subjected to repeated natural disturbances may be more vulnerable to anthropogenic stressors (e.g., overfishing). Alternatively, if an ecosystem has become adapted to a disturbance pattern, it may be affected when the disturbance is removed (fire-maintained grasslands). The lack of natural analogues makes it difficult to predict recovery from novel anthropogenic stressors such as exposure to synthetic chemicals.

The relative rate of recovery also can be estimated. For example, fish populations in a stream are likely to recover much faster from exposure to a degradable chemical than from habitat alterations resulting from stream channelization. It is critical to use knowledge of factors such as the temporal scales of organisms' life histories, the availability of adequate stock for recruitment, and the interspecific and trophic dynamics of the populations in evaluating the relative rates of recovery. A fisheries stock or forest might recover in several decades, a benthic infaunal community in years, and a planktonic community in weeks to months.

28.5 MANAGING RISK

When risk characterization is complete, a description of the risk assessment is communicated to the risk manager (Figure 28.1) to support a risk management decision. This communication usually is a report and might include:

- A description of risk assessor/risk manager planning results.
- A review of the conceptual model and the assessment end points.
- A discussion of the major data sources and analytical procedures used.
- A review of the stressor-response and exposure profiles.
- A description of risks to the assessment endpoints, including risk estimates and adversity evaluations.
- A summary of major areas of uncertainty and the approaches used to address them.
- A discussion of science policy judgments or default assumptions used to bridge information gaps, and the basis for these assumptions.

After the risk assessment is completed, risk managers may consider whether additional follow-up activities are required. Depending on the importance of the assessment, confidence level in the assessment results, and available resources, it may be advisable to conduct another iteration of the risk assessment in order to facilitate a final management decision. Ecological risk assessments are frequently designed in sequential tiers that proceed from simple, relatively inexpensive evaluations to more costly and complex assessments. Initial tiers are based on conservative assumptions, such as maximum exposure and ecological sensitivity. When an early tier cannot sufficiently define risk to support a management decision, a higher assessment tier that may require either additional data or applying more refined analysis techniques to available data may be needed. Higher tiers provide more ecologically realistic assessments while making less conservative assumptions about exposure and effects.

Another option is to proceed with a management decision based on the risk assessment and develop a monitoring plan to evaluate the results of the decision. For example, if the decision is to mitigate risks through exposure reduction, monitoring will help determine whether the desired reduction in exposure (and effects) is being achieved. Monitoring is also critical for determining the extent and nature of any ecological recovery that may be occurring.

Ecological risk assessment is important for environmental decision making because of the high cost of eliminating environmental risks associated with human activities and the necessity of making regulatory decisions in the face of uncertainty. Ecological risk assessment provides only a portion of the information required to make risk

management decisions, but this information is critical to scientifically defensible risk management. Thus ecological risk assessments should provide input to a diverse set of environmental decision-making processes, such as the regulation of hazardous waste sites, industrial chemicals, and pesticides, and improve the management of watersheds affected by multiple nonchemical and chemical stressors.

SUGGESTED READING

Bartell, S. M., R. H. Gardner, and R. V. O'Neill. *Ecological Risk Estimation*. Boca Raton, FL: Lewis Publishers, 1992.

Cardwell, R. D., B. R. Parkhurst, W. Warren-Hicks, and J. S. Volosin. Aquatic ecological risk. *Water Environ. Technol.* **5**: 47–51, 1993.

Harwell, M. A., W. Cooper, and R. Flaak. Prioritizing ecological and human welfare risks from environmental stresses. *Environ. Manag.* **16**: 451–464, 1992.

Kendall, R. J., T. E. Lacher, C. Bunck, B. Daniel, C. Driver, C. E. Grue, F. Leighton, W. Stansley, P. G. Watanabe, and M. Whitworth. An ecological risk assessment of lead shot exposure in non-waterfowl avian species: Upland game birds and raptors. *Environ. Toxicol. Chem.* **15**: 4–20, 1996.

National Research Council. A paradigm for ecological risk assessment. In *Issues in Risk Assessment*. Washington, DC: National Academy Press, 1993.

National Research Council. *Science and Judgment in Risk Assessment*. Washington, DC: National Academy Press, 1994.

National Research Council. *Understanding Risk: Informing Decisions in a Democratic Society*. Washington, DC: National Academy Press, 1996.

Ruckelshaus, W. D. Science, risk, and public policy. *Science* **221**: 1026–1028, 1983.

Solomon, K. R., D. B. Baker, R. P. Richards, K. R. Dixon, S. J. Klaine, T. W. La Point, R. J. Kendall, C. P. Weisskopf, J. M. Giddings, J. P. Geisy, L. W. Hall, W. M. Williams. Ecological risk assessment of atrazine in North American surface waters. *Environ. Toxicol. Chem.* **15**(1): 31–76, 1996.

Suter, G. W., II. Endpoints for regional ecological risk assessments. *Environ. Manag.* **14**: 19–23, 1990.

Suter, G. W., II. *Ecological Risk Assessment*. Boca Raton, FL: Lewis Publishers, 1993.

Suter, G. W., II. A critique of ecosystem health concepts and indexes. *Environ. Toxicol. Chem.* **12**: 1533–1539, 1993.

US Environmental Protection Agency. Summary report on issues in ecological risk assessment. Washington, DC: Risk Assessment Forum, USEPA, 1991. EPA/625/3-91/018.

US Environmental Protection Agency. Framework for ecological risk assessment. Washington, DC: Risk Assessment Forum, USEPA, 1992. EPA/630/R-92/001.

US Environmental Protection Agency. Peer review workshop report on a framework for ecological risk assessment. Washington, DC: Risk Assessment Forum, USEPA, 1992. EPA/625/3-91/022.

US Environmental Protection Agency. A review of ecological assessment case studies from a risk assessment perspective. Washington, DC: Risk Assessment Forum, USEPA, 1993. EPA/630/R-92/005.

US Environmental Protection Agency. Ecological risk assessment issue papers. Washington, DC: Risk Assessment Forum, USEPA, 1994. EPA/630/R-94/009.

US Environmental Protection Agency. Proposed guidelines for ecological risk assessment. Washington, DC: Risk Assessment Forum, USEPA, 1996. EPA/630/R-95/002B.