Chapter 24

Risk Assessment

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The task of interpreting data on the occurrence of pathogens in the environment is often critical in making decisions about potential health risks and corrective actions. Quantitative risk assessment (QRA) is an approach that allows the quantitative expression of risk in terms infection, illness or mortality from microbial pathogens. In this format, such information can be utilized by decision makers to determine the magnitude of such risks, and weigh the costs and benefits of corrective action. The purpose of this chapter is to provide a general background to the topic of risk analysis, and how it can be used in the problem-solving processes.

24.1 THE CONCEPT OF RISK ASSESSMENT

Risk, which is common to all life, is an inherent property of everyday human existence. It is therefore a key factor in all decision making. Risk assessment or analysis, however, means different things to different people: Wall Street analysts assess financial risks, and insurance companies calculate actuarial risks, while regulatory agencies estimate the risks of fatalities from nuclear plant accidents, the incidence of cancer resulting from industrial emissions and habitat loss associated with increases in human populations. All these seemingly disparate activities have in common the concept of a measurable phenomenon called risk that can be expressed in terms of probability. Thus, we can define risk assessment as the process of estimating both the probability that an event will occur, and the probable magnitude of its adverse effects—economic, health or safety related, or ecological—over a specified time period. For example, one might estimate the probable incidence of cancer in the community where a chemical was spilled over a period of years. Or one might calculate the health risks associated with the presence of pathogens in drinking water or food.

There are, of course, several varieties of risk assessment. Risk assessment as a formal discipline emerged in the 1940s and 1950s, paralleling the rise of the nuclear industry. Safety hazard analyses have been used since at least the 1950s in the nuclear, petroleum refining and chemical processing industries, as well as in aerospace. Health risk assessments, however, had their beginnings in 1986 with the publication of the "Guidelines for carcinogenic risk assessment" by the Environmental Protection Agency (EPA). Microbial risk assessment is relatively new, beginning in the mid-1980s, but has already been used in the development of government regulations (Regli *et al*., 1991).

24.2 ELEMENTS OF RISK ANALYSIS

Risk analysis framework has three basic components: risk assessment, risk management and risk communication (Figure 24.1). Chemical risk assessment has been used to judge the safety of our food and water supply. Such assessments are important in setting standards for chemical contaminants in the environment. Whether chemical or microbial, risk assessment consists of four basic steps:

- Hazard identification—Defining the hazard and nature of the harm: for example, identifying a contaminant

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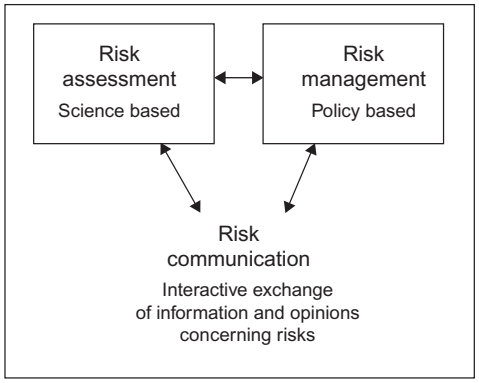


FIGURE 24.1 Risk analysis framework.

(e.g., a chemical, such as lead or carbon tetrachloride, or a microbial pathogen, such as *Legionella*), and documenting its toxic effects on humans.

- Exposure assessment—Determining the concentration of a contaminant in the environment and estimating its rate of intake. For example, determining the concentration of *Salmonella* in a meat product and the average dose a person would ingest.
- Dose–response assessment—Quantitating the adverse effects arising from exposure to a hazardous agent based on the degree of exposure. This assessment is usually expressed mathematically as a plot showing the response in living organisms to increasing doses of the agent (e.g., rotavirus).
- Risk characterization—Estimating the potential impact (e.g., human illness or death) of a microorganism or chemical based on the severity of its effects and the amount of exposure.

Once the risks are characterized, various regulatory options are evaluated in a process called risk management, which includes consideration of social, political and economic issues, as well as the engineering problems inherent in a proposed solution. One important component of risk management is risk communication, which is the interactive process of information and opinion exchange among individuals, groups and institutions. Risk communication includes the transfer of risk information from expert to nonexpert audiences. In order to be effective, risk communication must provide a forum for balanced discussions of the nature of the risk, lending a perspective that allows the benefits of reducing the risk to be weighed against the costs.

In the United States, the passage of federal and state laws to protect public health and the environment has expanded the application of risk assessment. Major federal agencies that routinely use risk analysis include the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA). Together with state agencies, these regulatory agencies use risk assessment in a variety of situations:

- Setting standards for concentrations of toxic chemicals or pathogenic microorganisms in water or food
- Assessing the risk from the release of genetically altered organisms
- Conducting baseline analyses of contaminated sites or facilities to determine the need for remediation and the extent of cleanup required
- Performing cost–benefit analyses of contaminated-site cleanup or treatment options (including treatment processes to reduce exposure to pathogens)
- Developing cleanup goals for contaminants for which no federal or state authorities have promulgated numerical standards: evaluating acceptable variance from promulgated standards and guidelines (e.g., approving alternative concentration limits)
- Constructing "what if" scenarios to compare the potential impact of remedial or treatment alternatives, and to set priorities for corrective action
- Evaluating existing and new technologies for effective prevention, control or mitigation of hazards and risks (e.g., new drinking water treatment technologies)
- Articulating community public health concerns and developing consistent public health expectations among different localities

Risk assessment provides an effective framework for determining the relative urgency of problems and the allocation of resources to reduce risks. Using the results of risk analyses, we can target prevention, remediation or control efforts toward areas, sources or situations in which the greatest risk reductions can be achieved with the resources available. However, risk assessment is not an absolute procedure carried out in a vacuum; rather, it is an evaluative, multifaceted, comparative process. Thus, to evaluate risk, we must inevitably compare one risk with a host of others. In fact, the comparison of potential risks associated with several problems or issues has developed into a subset of risk assessment called comparative risk assessment. Some commonplace risks are shown in Table 24.1. Here we see, for example, that risks from chemical exposure are fairly small compared with those associated with driving a car or smoking cigarettes.

Comparing different risks allows us to comprehend the uncommon magnitudes involved and to understand the level, or magnitude, of risk associated with a particular hazard. But comparison with other risks cannot itself establish the acceptability of a risk. Thus, the fact that the chance of death from a previously unknown risk is about the same as that from a known risk does not necessarily imply that the two risks are equally acceptable. Generally, comparing risks along a single dimension is not helpful when the risks are widely perceived as qualitatively different. Rather, we must take account of certain

TABLE 24.1 Examples of Some Commonplace Risks in the United States

Risk	Lifetime Risk of Mortality
Cancer from cigarette smoking (one pack per day)	1:4
Death in a motor vehicle accident	2:100
Homicide	1:100
Home accident deaths	1:100
Cancer from exposure to radon in homes	3:1000
Death from hepatitis A	3:1000
Exposure to the pesticide aflatoxin in peanut butter	6:10,000
Diarrhea from rotavirus	1:10,000
Exposure to typical EPA maximum chemical contaminant levels	1:10,000–1:10,000,000

Based on data in Wilson and Crouch (1987) and Gerba and Rose (1993).

qualitative factors that affect risk perception and evaluation when selecting risks to be compared. Some of these qualifying factors are listed in Table 24.2. We must also understand the underlying premise that voluntary risk is always more acceptable than involuntary risk. For example, the same people who cheerfully drive their cars every day—thus incurring a 2:100 lifetime risk of death by automobile—are quite capable of refusing to accept the 6:10,000 involuntary risk of eating peanut butter contaminated with aflatoxin.

In considering risk, then, we must also understand another principle—the *de minimis* principle, which means that there are some levels of risk so trivial that they are not worth bothering about. However attractive it is, this concept is hard to define, especially if we are trying to find a *de minimis* level acceptable to an entire society. Understandably, regulatory authorities are reluctant to be explicit about an "acceptable" risk. (How much aflatoxin would you consider acceptable in your peanut butter and jelly sandwich? How many dead insect parts?) Some prefer the term "tolerable risk," i.e., the level of risks we can accept given the economic costs, and social and scientific constraints. But it is generally agreed that a lifetime risk

TABLE 24.2 Factors Affecting Risk Perception and Risk Analysis

Factor	Conditions Associated with Increased Public Concern	Conditions Associated with Decreased Public Concern
Catastrophic potential	Fatalities and injuries grouped in time and space	Fatalities and injuries scattered and random
Familiarity	Unfamiliar	Familiar
Understanding	Mechanisms or process not understood	Mechanisms or process understood
Controllability (personal)	Uncontrollable	Controllable
Voluntariness of exposure	Involuntary	Voluntary
Effects on children	Children specifically at risk	Children not specifically at risk
Effects manifestation	Delayed effects	Immediate effects
Effects on future generations	Risk to future generations	No risk to future generations
Victim identity	Identifiable victims	Statistical victims
Dread	Effects dreaded	Effects not dreaded
Trust in institutions	Lack of trust in responsible institutions	Trust in responsible institutions
Media attention	Much media attention	Little media attention
Accident history	Major and sometimes minor accidents	No major or minor accidents
Equity	Inequitable distribution of risks and benefits	Equitable distribution of risks and benefits
Benefits	Unclear benefits	Clear benefits
Reversibility	Effects irreversible	Effects reversible
Origin	Caused by human actions or failures	Caused by acts of nature

From Covello et al. (1988).

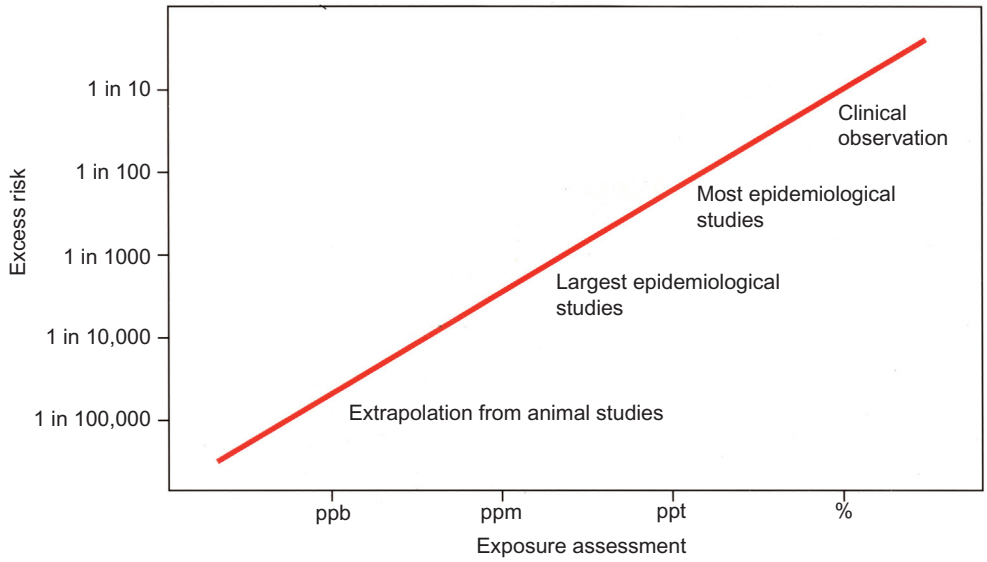


FIGURE 24.2 Sensitivity of epidemiology in detecting risks of regulatory concern. The generalized units of ppt (parts per thousand), ppm (parts per million), ppb (parts per billion), and % (parts per hundred) are used here for comparative purposes. Modified from National Research Council (1993).

on the order of one in a million (or 10^{-6}) is trivial enough to be acceptable for the general public. Although the origins and precise meaning of a one-in-a-million acceptable risk remain obscure, its impact on product choices, operations and costs is very real, for example, hundreds of billions of dollars in hazardous waste site cleanup decisions alone. The levels of acceptable risk can vary within this range. Levels of risk at the higher end of the range (10^{-4} rather than 10^{-6}) may be acceptable if only a few people are exposed rather than the entire populace. For example, workers dealing with production of solvents can often tolerate higher levels of risk than can the public at large. These higher levels are justified because workers tend to be a relatively homogeneous, healthy group, and because employment is voluntary; however, the level of risks would not be acceptable for the same solvents for the general population.

24.3 THE PROCESS OF RISK ASSESSMENT

24.3.1 Hazard Identification

The first step in risk assessment is to determine the nature of the hazard. For pollution-related problems, the hazard in question is usually a specific chemical, a physical agent (such as irradiation), or a microorganism identified with a specific illness or disease. Thus, the hazard identification component of a pollution risk assessment consists of a review of all relevant biological and chemical information bearing on whether or not an agent poses a specific threat.

As Figure 24.2 shows, clinical studies of disease can be used to identify high risks (between 1:10 and 1:100), whereas most epidemiological studies can detect risks down to 1:1000, and very large epidemiological studies can examine risks in the 1:10,000 range. However, risks lower than 1:10,000 cannot be studied with much certainty using epidemiological approaches. Because regulatory policy objectives generally strive to limit risks below 1:100,000 for life-threatening diseases such as cancer, these lower risks are often estimated by extrapolating from the effects of high doses given to animals.

24.3.2 Exposure Assessment

Exposure assessment is the process of measuring or estimating the intensity, frequency and duration of human exposures to an environmental agent. Exposure to contaminants can occur via inhalation, ingestion of water or food, or the skin. Contaminant sources, release mechanisms, transport and transformation characteristics are all important aspects of exposure assessment, as are the nature, location and activity patterns of the exposed population. (This explains why it is critical to understand the factors and processes influencing the transport and fate of a contaminant.)

An exposure pathway is the course that a hazardous agent takes from a source to a receptor (e.g., human or animal) via environmental carriers or media—generally, air (volatile compounds, particles) or water (soluble or colloidal compounds). An exception is electromagnetic radiation, which needs no medium. The exposure route, or intake pathway, is the mechanism by which the transfer occurs—usually by inhalation, ingestion and/or dermal contact (Figure 24.3). Direct contact can result in a local effect at the point of entry, and/or in a systemic effect.

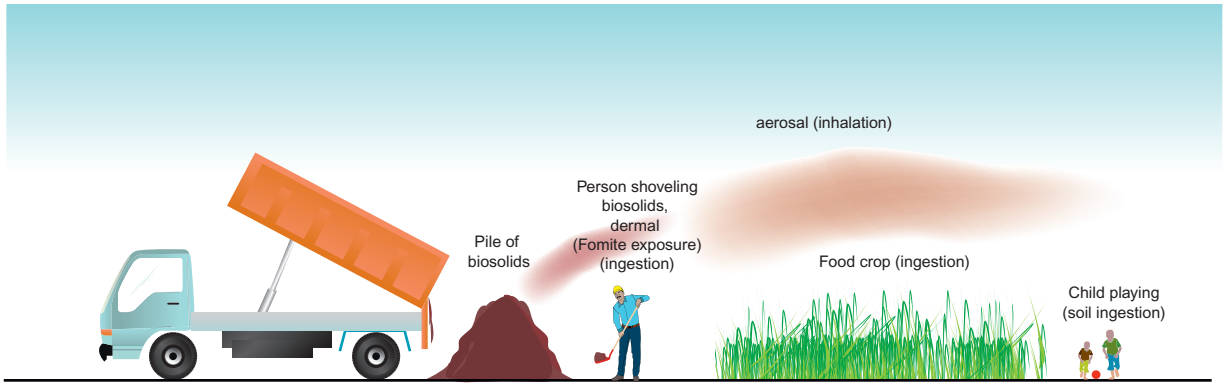


FIGURE 24.3 Potential routes of pathogen exposure from land application of biosolids.

The quantitation of exposure, intake or potential dose can involve equations with three sets of variables:

- Concentrations of chemicals or microbes in the media
- Exposure rates (magnitude, frequency, duration)
- Quantified biological characteristics of receptors (e.g., body weight, absorption capacity for chemicals, level of immunity to microbial pathogens)

Exposure concentrations are derived from measured, monitored and/or modeled data. Ideally, exposure concentrations should be measured at the points of contact between the environmental media and current or potential receptors. It is usually possible to identify potential receptors and exposure points from field observations and other information. However, it is seldom possible to anticipate all potential exposure points, and measure all environmental concentrations under all conditions. In practice, a combination of monitoring and modeling data, together with a great deal of professional judgment, is required to estimate exposure concentrations.

In order to assess exposure rates via different pathways, one has to consider and weigh many factors. For example, in estimating exposure to a substance via drinking water, one first has to determine the average daily consumption of that water. But this is not as easy as it sounds. Studies have shown that daily fluid intake varies greatly from individual to individual. Moreover, total water intake depends on how much fluid is consumed as tap water, and how much is ingested in the form of soft drinks and other nontap water sources. Tap water intake also changes significantly with age, body weight, diet and climate. Because these factors are so variable, the EPA has suggested a number of very conservative "default" exposure values that can be used when assessing contaminants in tap water, vegetables, soil and the like (see Table 24.3).

One also has to consider how much of the population to include in the exposure. For example, the average consumption of tap water is 1.5 liters/day; some persons drink less than this and some significantly more. Approximately 95% of the population consumes 2 liters or less. If we assume the exposure to be 1.5 liters/day, then we are excluding half the population, which consumes more than this amount. Using the 2 liter/day value allows inclusion of 95% of the population.

Event trees have been used to estimate exposures (see Example Calculation 24.1). Event trees are useful to estimate exposure by analysis of pathogen loads upstream, when the actual concentration of the harmful agent that reaches the target is too low to measure.

24.3.3 Dose–Response Assessment

All chemical and microbial contaminants are not equal in their capacity to cause adverse effects. To determine the capacity of agents to cause harm, we need quantitative toxicity or infectivity data. These data can sometimes be derived from occupational, clinical and epidemiological studies. Most toxicity data, however, come from animal experiments in which researchers expose laboratory animals, mostly mice and rats, to increasingly higher concentrations or doses, and observe their corresponding effects. The result of these experiments is the dose–response relationship—a quantitative relationship that indicates the agent's degree of toxicity to exposed species. Dose is normalized as milligrams of substance, or number of organisms ingested, inhaled or absorbed (in the case of chemicals) through the skin per kilogram of body weight per day (mg/kg/day). Responses or effects can vary widely—from no observable effect, to temporary and reversible effects (e.g., enzyme depression caused by some pesticides or diarrhea caused by viruses), to permanent organ injury (e.g., liver and kidney damage caused by chlorinated solvents, heavy metals or viruses), to chronic functional impairment (e.g., bronchitis or emphysema arising from smoke damage), to death.

TABLE 24.3 EPA Standard Default Exposure Factors

Land Use	Exposure Pathway	Daily Intake	Exposure Frequency (days/year)	Exposure Duration (years)
Residential	Ingestion of potable water	2 liters/day	350	30
	Ingestion of soil and dust	200 mg (child)	350	6
		100 mg (adult)		24
	Inhalation of contaminants	20 m^3 (total)	350	30
		15 m^3 (indoor)		
Industrial and commercial	Ingestion of potable water	1 liter	250	25
	Ingestion of soil and dust	50 mg	250	25
	Inhalation of contaminants	20 m^3 (workday)	250	25
Agricultural	Consumption of homegrown produce	42 g (vegetable) (fruit 80 g)	350	30
Recreational	Consumption of locally caught fish	54 g	350	30
Swimming		10–100 ml[a]	1–10	–

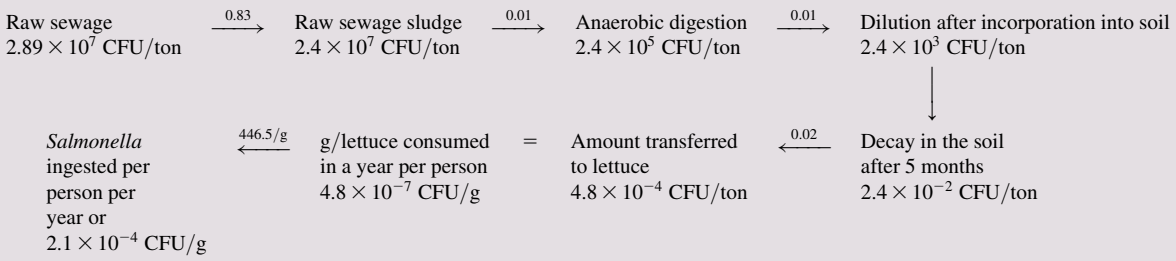
Modified from Kolluru (1993).
[a]*Per event.*

Example Calculation 24.1 Estimating Exposure: Application of Event Trees

Event trees can be used to simplify the process of modeling the various pathways and visualizing how the infectivity of a pathogen changes through various processes and routes of exposure (Gale, 2003; Stine *et al.*, 2005). Often times the concentration of the pathogen is unknown in the media to which an individual or population may be exposed. In addition, the exposed concentration may be at levels that cannot be measured (e.g., below the detection limit of the method employed). Through the use of an event tree, an estimate can be made of the amount of pathogen in the media to which an individual may be exposed, and the uncertainties defined. Event trees are also useful in determining where the greatest amount of uncertainty may exist (die-off fate in the soil, transfer from the soil to plants, etc.).

The following is an example of an event tree used to estimate the exposure of *Salmonella* from biosolids applied to a food crop.

Event tree for estimating exposure from *Salmonella* when biosolids are used on farmland to grow lettuce (numbers above arrows show percent reductions in pathogen load for a given event):



The goal of a dose–response assessment is to obtain a mathematical relationship between the amount (concentration) of a toxicant or microorganism to which a human is exposed and the risk of an adverse outcome from that dose. The data resulting from experimental studies are presented as a dose–response curve, as shown in Figure 24.4. The ordinate represents the dose and the abscissa represents the risk that some adverse health effect will occur. In the case of a pathogen, for instance, the ordinate may represent the risk of infection and not necessarily illness.

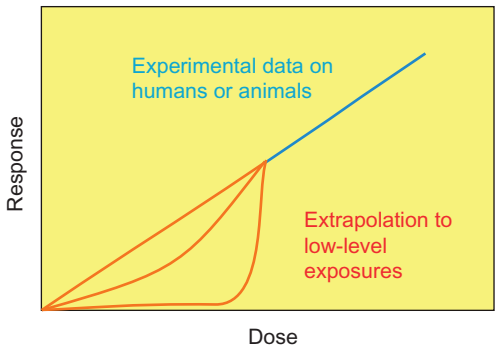


FIGURE 24.4 Extrapolation of dose–response curves. Adapted from U.S. EPA (1990).

However, dose–response curves derived from animal studies must be interpreted with care. The data for these curves are necessarily obtained by examining the effects of large doses on test animals. This is because the large costs involved in testing limits the numbers of animals that can be used—it is both impractical and cost prohibitive to use thousands (even millions) of animals to observe just a few individuals that show adverse effects at low doses (e.g., risks of 1:1000 or 1:10,000). Researchers must therefore extrapolate low-dose responses from their high-dose data. And therein lies the rub: dose–response curves are subject to controversy because their results change depending on the method chosen to extrapolate from the high doses actually administered to laboratory test subjects, to the low doses humans are likely to receive in the course of everyday living.

This controversy revolves around the choice of mathematical models that have been proposed for extrapolation to low doses. Unfortunately, since there are no data available to validate these models, they cannot be proved or disproved, and so there is no way to know which model is the most accurate. The choice of models is therefore strictly a policy decision, which is usually based on understandably conservative assumptions. Thus, for noncarcinogenic chemical responses, the assumption is that some threshold exists below which there is no toxic response; that is, no adverse effects will occur below some very low dose (say, one in a million). Carcinogens, however, are considered nonthreshold—that is, the conservative assumption is that exposure to any amount of carcinogen creates some likelihood of cancer. This means that the only "safe" amount of carcinogen is zero, so the dose–response plot is required to go through the origin (0), as shown in Figure 24.4.

In the microbiological literature the term "minimum infectious dose" is used frequently, implying that a threshold dose exists for microorganisms. In reality, the term used usually refers to the ID_{50} or the dose at which 50% of the animals or humans exposed became infected or exhibit any symptoms of an illness. Existing infectious dose data are compatible with nonthreshold responses, and the term "infectivity" is probably more appropriate when referring to differences in the likelihood of an organism causing an infection. For example, the probability of a given number of ingested rotaviruses causing diarrhea is greater than that for *Salmonella.* Thus, the infectivity of rotavirus is greater than that of *Salmonella.*

There are many mathematical models to choose from for modeling risk. These include the one-hit model, the multistage model, the multihit model and the probit model. The characteristics of these models for nonthreshold effects are listed in Tables 24.4 and 24.5.

TABLE 24.4 Primary Models Used for Assessment of Nonthreshold Effects[a]

Model	Comments
One hit	Assumes (1) single stage for cancer, (2) malignant change induced by one molecular or radiation interaction. *Very conservative.*
Linear multistage	Assumes multiple stages for cancer. *Fits curve to the experimental data.*
Multihit	Assumes several interactions needed before cells become transformed. *Least conservative model.*
Probit	Assumes probit (lognormal) distribution for tolerances of exposed population. *Appropriate for acute toxicity; questionable for cancer.*

Modified from Cockerham and Shane (1994).
[a]*All the models assume that exposure to the pollutant will always produce an effect, regardless of dose.*

TABLE 24.5 Lifetime Risks of Cancer Derived from Different Extrapolation Models[a]

Model Applied	Lifetime Risk (mg/kg/day) from Toxic Chemical
One hit	6.0×10^{-5} (1 in 17,000)
Multistage	6.0×10^{-6} (1 in 167,000)
Multihit	4.4×10^{-7} (1 in 2.3 million)
Probit	1.9×10^{-10} (1 in 5.3 billion)

From U.S. EPA (1990).
[a]*All risks are for a full lifetime of daily exposure. The lifetime is used as the unit of risk measurement because the experimental data reflect the risk experienced by animals over their full lifetimes. The values shown are upper confidence limits on risks.*

24.3.4 Risk Characterization

24.3.4.1 Uncertainty Analysis

Uncertainty is inherent in every step of the risk assessment process. Thus, before we can begin to characterize any risk, we need some idea of the nature and magnitude of uncertainty in the risk estimate. Sources of uncertainty include:

- Extrapolation from high to low doses
- Extrapolation from animal to human responses
- Extrapolation from one route of exposure to another
- Limitations of analytical methods to measure the organism
- Estimates of exposure

Although the uncertainties are generally much larger in estimates of exposure and the relationships between dose and response (e.g., the percent mortality), it is important to include the uncertainties originating from all steps in a risk assessment as part of risk characterization.

Two approaches commonly used to characterize uncertainty are sensitivity analyses and Monte Carlo simulations. In sensitivity analyses, the uncertain quantities of each parameter (e.g., average values, high and low estimates) are varied, usually one at a time, to find out how changes in these quantities affect the final risk estimate. This procedure gives a range of possible values for the overall risk and provides information on which parameters are most crucial in determining the size of the risk. In a Monte Carlo simulation, however, it is assumed that all parameters are random or uncertain. Thus, instead of varying one parameter at a time, a computer program is used to select distributions randomly every time the model equations are solved, the procedure being repeated many times. The resulting output can be used to identify values of exposure or risk corresponding to a specified probability, say the 50th percentile or 95th percentile. Details of these methods of dealing with uncertainty can be found in the text *Quantitative Microbial Risk Assessment* (Haas *et al*., 2014).

24.3.4.2 Risk Projection and Management

The final phase of the risk assessment process is risk characterization. In this phase, exposure and dose−response assessments are integrated to yield probabilities of effects occurring in humans under specific exposure conditions. Quantitative risks are calculated for appropriate media (air, water, food) and pathways. For example, the risks of lead in water are estimated over a lifetime assuming:

1. that the exposure is 2 liters of water ingested over a 70-year lifetime; and
2. that different concentrations of lead occur in the drinking water

This information can be used by risk managers to develop standards or guidelines for specific toxic chemicals or infectious microorganisms in different media, such as the drinking water or food supply.

In the case of a microorganism, a treatment strategy may be used. For example, 99.9% removal of *Giardia* cysts is required for drinking water treatment plants in the United States to ensure that the yearly risk of infection in a community is no greater than 1:10,000. The assumption is made that this amount of removal will guarantee a concentration of *Giardia* cysts in the finish water that would not result in a risk greater than 1:10,000 (Gerba *et al*., 1997; Teunis *et al*., 1997)

24.4 MICROBIAL RISK ASSESSMENT

Outbreaks of waterborne disease caused by microorganisms usually occur when the water supply has been obviously and significantly contaminated. In such high-level cases, the exposure is manifest, and cause and effect are relatively easy to determine. However, exposure to low-level microbial contamination is difficult or impossible to determine epidemiologically. We know, for example, that long-term exposure to microbes can have a significant impact on the health of individuals within a community, but we need a way to measure that impact.

For some time, methods have been available to detect the presence of low levels (one organism per 1000 liters) of pathogenic organisms in water, including enteric viruses and protozoan parasites. The trouble is that the risks posed to the community by these low levels of pathogens in a water supply over time are not like those posed by low levels of chemical toxins or carcinogens. For example, it takes just one amoeba in the wrong place at the wrong time to infect one individual, whereas the same individual would have to consume some quantity of a toxic chemical to be comparably harmed. Microbial risk assessment is, therefore, a process that allows us to estimate responses in terms of the *risk of infection* in a quantitative fashion. Microbial risk generally follows the steps used in other health-based risk assessments—hazard identification, exposure assessment, dose−response and risk characterization. The differences are in the specific assumptions, models and extrapolation methods used. The United States Environmental Protection Agency and the United States Department of Agriculture have developed a guidance document for the conduct of microbial risk assessments for water and food (USEPA, 2012).

Hazard identification in the case of pathogens is complicated because several outcomes—from asymptomatic infection to death (Figure 24.5)—are possible, and these

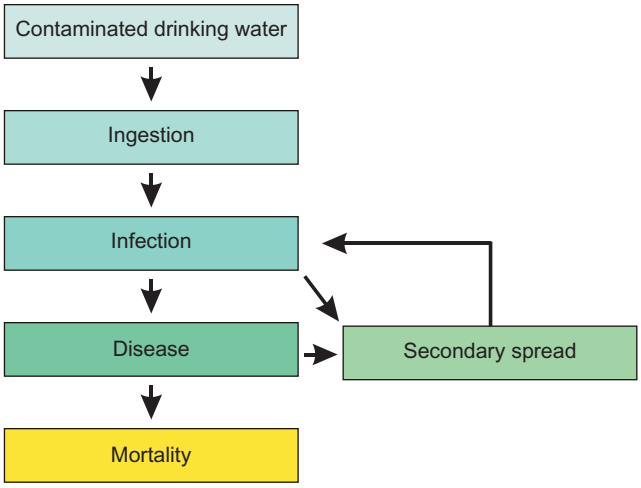


FIGURE 24.5 Outcomes of enteric viral exposure.

outcomes depend on the complex interaction between the pathogenic agent (the "infector") and the host (the "infectee"). This interaction, in turn, depends on the characteristics of the host as well as the nature of the pathogen. Host factors, for example, include: preexisting immunity; age; nutrition; ability to mount an immune response; and other nonspecific host factors. Agent factors include type and strain of the organism, as well as its capacity to elicit an immune response.

Among the various outcomes of infection is the possibility of subclinical infection. Subclinical (asymptomatic) infections are those in which the infection (growth of the microorganism within the human body) results in no obvious illness such as fever, headache or diarrhea. That is, individuals can host a pathogen microorganism—and transmit it to others—without ever getting sick themselves. The ratio of clinical to subclinical infection varies from pathogen to pathogen as shown in Table 24.6. Poliovirus infections, for instance, seldom result in obvious clinical symptoms; in fact, the proportion of individuals developing clinical illness may be less than 1%. However, other enteroviruses, such as the Coxsackieviruses, may exhibit a greater proportion. In many cases, such as for rotaviruses, the probability of developing clinical illness appears to be completely unrelated to the dose an individual receives via ingestion (Ward *et al.*, 1986). Rather, the likelihood of developing clinical illness depends on the type and strain of the virus as well as host age, nonspecific host factors and possibly preexisting immunity. The incidence of clinical infection can also vary from year to year for the same virus, depending on the emergence of new strains or genotypes.

Another outcome of infection is the development of clinical illness. Several host factors play a major role in this outcome. The age of the host is often a determining factor. In the case of hepatitis A, for example, clinical illness can vary from about 5% in children younger than 5 years of age to 75% in adults. In contrast, children are more likely to develop rotaviral gastroenteritis than are adults. Immunity is also an important factor, albeit a variable one. That is, immunity may or may not provide long-term protection from reinfection, depending on the enteric pathogen. It does not, for example, provide long-term protection against the development of clinical illness in the case of the Norovirus or *Giardia*. However, for most enteroviruses and for the hepatitis A virus, immunity to reinfection is believed to be lifelong. Other undefined host factors may also control the odds of developing illness. For example, in experiments with Norovirus, human volunteers who did not become infected upon an initial exposure to the virus also did not respond to a second exposure. In contrast, volunteers who developed gastroenteritis upon the first exposure also developed illness after the second exposure.

The ultimate outcome of infection—mortality—can be caused by nearly all enteric organisms. The factors that control the prospect of mortality are largely the same factors that control the development of clinical illness. Host age, for example, is significant. Thus, mortality for hepatitis A and poliovirus is greater in adults than in children. In general, however, one can say that the very young, the

TABLE 24.6 Ratio of Subclinical Infections with Enteric Viruses

Virus	Frequency of Clinical Illness[a] (%)
Poliovirus 1	0.1–1
Coxsackie	
A16	50
B2	11–50
B3	29–96
B4	30–70
B5	5–40
Echovirus	
Overall	50
9	15–60
18	Rare–20
20	33
25	30
30	50
Hepatitis A virus (adults)	75
Rotavirus	
Adults	56–60
Children	28
Astrovirus (adults)	12.5

From Gerba and Rose (1993).
[a]*The percentage of the individuals infected who develop clinical illness.*

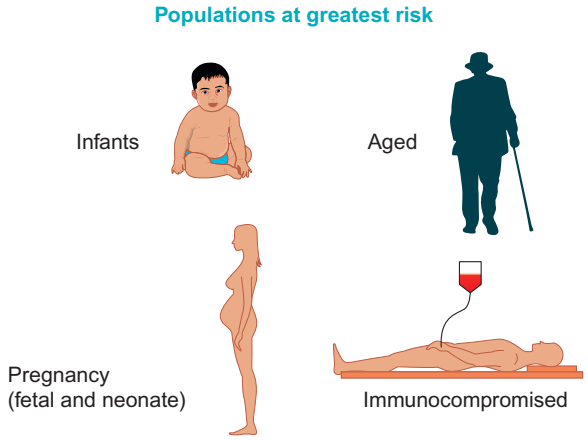


FIGURE 24.6 Populations at greatest risk of serious illness and mortality from pathogens.

TABLE 24.7 Case–Fatality Rates Observed for Enteric Pathogens in Nursing Home versus General Population

Organism	Case–fatality Rate (%) in General Population	Case–fatality Rate (%) in Nursing Homes
Campylobacter jejuni	0.1	1.1
Escherichia coli O157:H7	0.2	11.8
Salmonella	0.1	3.8
Rotavirus	0.01	1.0

Modified from Gerba et al. (1996).

TABLE 24.8 Case–Fatality Rates for Enteric Viruses and Bacteria

Organism	Case–fatality Rate (%)
Viruses	
Poliovirus 1	0.90
Coxsackie	
A2	0.50
A4	0.50
A9	0.26
A16	0.12
Coxsackie B	0.59–0.94
Echovirus	
6	0.29
9	0.27
Hepatitis A	0.30
Rotavirus	
Total	0.01
Hospitalized	0.12
Bacteria	
Shigella	0.2
Salmonella	0.1
Escherichia coli O157:H7	0.2
Campylobacter jejuni	0.1

From Gerba and Rose (1993) and Gerba et al. (1995).

elderly and the immunocompromised are at the greatest risk of a fatal outcome of most illnesses (Figure 24.6) (Gerba *et al.*, 1996). For example, the case–fatality rate (%) for *Salmonella* in the general population is 0.1%, but it has been observed to be as high as 3.8% in nursing homes (Table 24.7). In North America and Europe, the reported case–fatality rates (i.e., the ratio of cases to fatalities reported as a percentage of persons who die) for enterovirus infections range from less than 0.1 to 0.94%, as shown in Table 24.8. The case–fatality rate for common enteric bacteria ranges from 0.1 to 0.2% in the general population. Enteric bacterial diseases can be treated with antibiotics, but no treatment is available for enteric viruses.

Recognizing that microbial risk involves a myriad of pathogenic organisms capable of producing a variety of outcomes that depend on a number of factors—many of which are undefined—one must now face the problem of exposure assessment, which has complications of its own. Unlike chemical-contaminated water, microorganism-contaminated water does not have to be consumed to cause harm. That is, individuals who do not actually drink, or even touch, contaminated water also risk infection because pathogens—particularly viruses—may be spread by person-to-person contact or subsequent contact with contaminated inanimate objects (such as toys). This phenomenon is described as the secondary attack rate, which is reported as a percentage. For example, one person infected with poliovirus can transmit it to 90% of the persons with whom they associate. This secondary spread of viruses has been well documented for waterborne outbreaks of several diseases, including that caused by Norovirus, whose secondary attack rate is about 30%.

The question of dose is another problem in exposure assessment. How does one define "dose" in this context? To answer this question, researchers have conducted a number of studies to determine the infectious dose of enteric microorganisms in human volunteers. Such human experimentation is necessary because determination of the infectious dose in animals and extrapolation to humans is often impossible. In some cases, for example, humans are

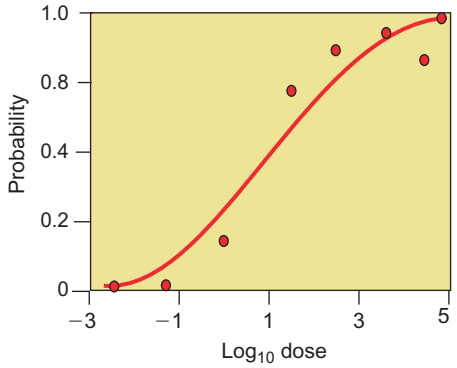


FIGURE 24.7 Dose–response for human rotavirus by oral ingestion.

the primary or only known host. In other cases, such as that of *Shigella* or Norovirus, infection can be induced in laboratory-held primates, but it is not known whether the infectious dose data can be extrapolated to humans. Much of the existing data on infectious doses of viruses has been obtained with attenuated vaccine viruses, or with avirulent laboratory-grown strains, so that the likelihood of serious illness is minimized. An example of a dose–response curve for a human feeding study with rotavirus is shown in Figure 24.7. Information can also be used from food or waterborne outbreaks if the number of organisms ingested in the food or water is known. Use of such data suggests that the doses needed for infection and disease are lower than indicted from controlled human feeding experiments, probably reflecting differences in virulence of the organisms, and heterogeneity in outcome among a diverse population (i.e., varying degrees of inherent susceptibility) (Teunis *et al.*, 2004).

Next, one must choose a dose–response model, whose ordinate is the dose and whose abscissa is the risk of infection (see Figure 24.7). The choice of model is critical so that risks are not greatly over- or underestimated. A modified exponential (beta–Poisson distribution) or a log-probit (simple lognormal, or exponential, distribution) model is commonly used to describe the probability of infection in human subjects for many enteric microorganisms (Haas, 1983). These models have been found to best fit the experimental data. Both are nonthreshold models. For the beta–Poisson model the probability of infection from a single exposure, P, can be described as follows:

$$P = 1 - (1 + N/\beta)^{-\alpha} \qquad \text{(Eq. 24.1)}$$

where N is the number of organisms ingested per exposure and α and β represent parameters characterizing the host–virus interaction (dose–response curve). Some values for α and β for several enteric waterborne pathogens are shown in Table 24.9; these values were determined from human studies. For some microorganisms, an exponential model may better represent the probability of infection.

TABLE 24.9 Best Fit Dose–Response Parameters for Enteric Pathogens Ingestion Studies

Agent	Best Model	Model Parameters
Echovirus 12	Beta–Poisson	$\alpha = 0.374$ $\beta = 186.69$
Rotavirus	Beta–Poisson	$\alpha = 0.26$ $\beta = 0.42$
Poliovirus 1	Exponential	$r = 0.009102$
Poliovirus 1	Beta–Poisson	$\alpha = 0.1097$ $\beta = 1524$
Poliovirus 3	Beta–Poisson	$\alpha = 0.409$ $\beta = 0.788$
Cryptosporidium	Exponential	$r = 0.004191$
Giardia lamblia	Exponential	$r = 0.02$
Salmonella	Exponential	$r = 0.00752$
Escherichia coli	Beta–Poisson	$\alpha = 0.1705$ $\beta = 1.61 \times 10^6$

Modified from Regli et al. (1991).

$$P = 1 - \exp(-rN) \qquad \text{(Eq. 24.2)}$$

In this equation, r is the fraction of the ingested microorganisms that survive to initiate infections (host–microorganism interaction probability). Table 24.9 shows examples of results of both models for several organisms.

These models define the probability of the microorganism overcoming the host defenses (stomach pH, finding a susceptible cell, nonspecific immunity, etc.) to establish an infection in the host. When one uses these models, one estimates the probability of becoming infected after ingestion of various concentrations of pathogen. For example, Case Study 24.1 shows how to calculate the risk of acquiring a viral infection from consumption of contaminated drinking water containing echovirus 12 using Eq. 24.1.

Annual and lifetime risks can also be determined, again assuming a Poisson distribution of the virus in the water consumed (assuming daily exposure to a constant concentration of viral contamination), as follows:

$$P_A = 1 - (1 - P)^{365} \qquad \text{(Eq. 24.3)}$$

where P_A is the annual risk (365 days) of contracting one or more infections; and

$$P_L = 1 - (1 - P)^{25{,}550} \qquad \text{(Eq. 24.4)}$$

where P_L is the lifetime risk (assuming a lifetime of 70 years = 25,550 days) of contracting one or more infections.

Case Study 24.1 Application of a Virus Risk Model to Characterize Risks from Consuming Shellfish

It is well known that infectious hepatitis and viral gastroenteritis are caused by consumption of raw or, in some cases, cooked clams and oysters. The concentration of echovirus 12 was found to be 8 plaque-forming units (PFU) per 100 g in oysters collected from coastal New England waters. What are the risks of becoming infected and ill from echovirus 12 if the oysters are consumed? Assume that a person usually consumes 60 g of oyster meat in a single serving:

If there are 8 PFU per 100 g of oyster, then for 60 g of oyster, $N = 4.8$ PFU consumed

From Table 24.9, $\alpha = 0.374$, $\beta = 186.69$. The probability of infection from Eq. 24.1 is then

$$P = 1\left(1+4.8/186.69\right)^{-0.374} = 9.4\times10^{-3}$$

If the percentage of infections that result in risk of clinical illness is 50%, then from Eq. 24.5 one can calculate the risk of clinical illness:

$$\text{Risk of clinical illness} = (9.4\times10^{-3})(0.50) = 4.7\times10^{-3}$$

If the case-fatality rate is 0.001%, then from Eq. 24.6:

$$\text{Risk of mortality} = (9.4\times10^{-3})(0.50)(0.001) = 4.7\times10^{-6}$$

If a person consumes oysters 10 times a year with 4.8 PFU per serving, then one can calculate the risk of infection in 1 year from Eq. 24.3:

$$\text{Annual risk} = P_A = 1-(1-9.4\times10^{-3})^{365} = 9.7\times10^{-1}$$

Risks of clinical illness and mortality can then be determined by incorporating terms for the percentage of clinical illness and mortality associated with each particular virus:

$$\text{Risk of clinical illness} = PI \qquad \text{(Eq. 24.5)}$$

$$\text{Risk of mortality} = PIM \qquad \text{(Eq. 24.6)}$$

where I is the percentage of infections that result in clinical illness and M is the percentage of clinical cases that result in mortality.

Application of this model allows estimation of the risks of infection, development of clinical illness and mortality for different levels of exposure. As shown in Table 24.10, for example, the estimated risk of infection from one rotavirus in 100 liters of drinking water (assuming ingestion of 2 liters per day) is 1.2×10^{-3}, or almost one in a thousand (1:1000) for a single-day exposure. This risk would increase to 3.6×10^{-1}, or approximately one in three, on an annual basis. As can be seen from this table, the risk of developing of clinical illness also appears to be significant for exposure to low levels of rotavirus in drinking water. Example Calculation 24.2 illustrates an example of a calculation for a risk assessment for rotavirus in drinking water.

TABLE 24.10 Risk of Infection, Disease and Mortality for Rotavirus

Virus Concentration per 100 liters	Daily Risk	Annual Risk
Infection		
100	9.6×10^{-2}	1.0
1	1.2×10^{-3}	3.6×10^{-1}
0.1	1.2×10^{-4}	4.4×10^{-2}
Disease		
100	5.3×10^{-2}	5.3×10^{-1}
1	6.6×10^{-4}	2.0×10^{-1}
0.1	6.6×10^{-5}	2.5×10^{-2}
Mortality		
100	5.3×10^{-6}	5.3×10^{-5}
1	6.6×10^{-8}	2.0×10^{-5}
0.1	6.6×10^{-9}	2.5×10^{-6}

Modified from Gerba and Rose (1993).

Example Calculation 24.2 Risk Assessment for Rotavirus in Drinking Water

Pathogen Identified	**Rotavirus**
↓	↓
Dose–Response Model (based on human ingestion studies)	Best fit for data is the Beta–Poisson Model $P = (1 + N/\beta)^{-\alpha}$ $\alpha = 0.2631$ $\beta = 0.42$
↓	↓
Exposure (field studies on concentration in drinking water)	4 rotavirus/1000 liters
↓	↓
Risk Characterization	Risk of Infection Assumes: 2 liters/day of drinking water ingested. Thus, $N = 0.008$/day Risk of Infection/day = 1:200 Risk of Infection/year $P_A = 1-(1-P)^{365}$ $P_A = 1{:}2$

The EPA has recommended that any drinking water treatment process should be designed to ensure that

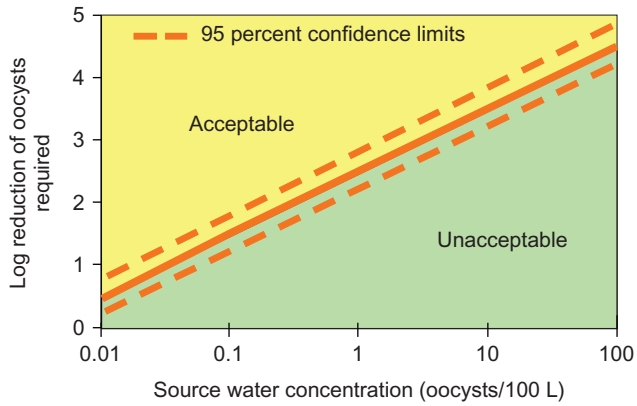


FIGURE 24.8 Relationship of influent *Cryptosporidium* concentration and log reduction by treatment necessary to produce acceptable water. Data from Haas *et al*. (1996).

human populations are not subjected to risk of infection greater than 1:10,000 for a yearly exposure. To achieve this goal, it would appear from the data shown in Table 24.10 that the virus concentration in drinking water would have to be less than one per 1000 liters. Thus, if the average concentration of enteric viruses in untreated water is 1400/1000 liters, treatment plants should be designed to remove at least 99.99% of the virus present in the raw water. A further application of this approach is to define the required treatment of a water source in terms of the concentration of a disease-causing organism in that supply. Thus, the more contaminated the raw water source, the more treatment is required to reduce the risk to an acceptable level. An example of this application is shown in Figure 24.8. The plausibility of validation of microbial risk assessment models has been examined by using data from foodborne outbreaks in which information has been available on exposure and outcomes (Rose *et al*., 1995; Crockett *et al*., 1996). These studies suggest that microbial risk assessment can give reasonable estimates of illness from exposure to contaminated foods (Table 24.11).

In summary, risk assessment is a major tool for decision making in the regulatory arena. This approach is used to explain chemical and microbial risks as well as ecosystem impacts. The results of such assessments can be used to inform risk managers of the probability and extent of environmental impacts resulting from exposure to different levels of stress (contaminants). Moreover, this process, which allows the quantitation and comparison of diverse risks, lets risk managers utilize the maximum amount of complex information in the decision-making process. This information can also be used to weight the cost and benefits of control options and to develop standards or treatment options (see Case Study 24.2).

TABLE 24.11 Comparison of Outbreak Data to Model Predictions for Assessment of Risks Associated with Exposure to *Salmonella*

Food	Dose (CFU)	Amount Consumed	Attack Rate (%)	Predicted *P* (%)
Water	17	1 liter	12	12
Pancretin	200	7 doses	100	77
Ice cream	102	1 portion	52	54
Cheese	100–500	28 g	28–36	53–98
Cheese	10^5	100 g	100	>99.99
Ham	10^6	50–100 g	100	>99.99

Modified from Rose et al. *(1995).*

QUESTIONS AND PROBLEMS

1. What are some differences between the risks posed by chemicals and those posed by microorganisms?
2. What are some of the potential applications of risk assessment?
3. What is the difference between risk assessment and risk management?
4. Why is the selection of the dose–response curve so important in risk assessment?
5. What is meant by a threshold dose–response curve? Give arguments for a threshold and a nonthreshold dose–response curve for microorganisms.
6. What is the difference between a voluntary and an involuntary risk? Give examples of both.
7. List the four steps in a formal health risk assessment.
8. Does infection always lead to illness with enteric pathogens? What are the factors that determine morbidity and mortality outcomes with microbial infections?
9. What types of dose–response curve best reflect pathogen exposure?
10. What are some potential applications of microbial risk assessment?
11. Calculate the risk of infection from rotavirus during swimming in polluted water. Assume that 50 ml of water is ingested during swimming and the concentration of virus was one per 10 liters. What would the risk be in a year if a person went swimming 10 times in the same water with the same concentration of rotavirus?

Case Study 24.2 How Do We Set Standards for Pathogens in Drinking Water?

In 1974 the U.S. Congress passed the Safe Drinking Water Act giving the U.S. Environmental Protection Agency the authority to establish standards for contaminants in drinking water. Through a risk analysis approach, standards have been set for many chemical contaminants in drinking water. Setting standards for microbial contaminants proved more difficult because (1) methods for the detection of many pathogens are not available, (2) days to weeks are sometimes required to obtain results, and (3) costly and time-consuming methods are required. To overcome these difficulties, coliform bacteria had been used historically to assess the microbial quality of drinking water. However, by the 1980s it had become quite clear that coliform bacteria did not indicate the presence of pathogenic waterborne *Giardia* or enteric viruses. Numerous outbreaks had occurred in which coliform standards were met, because of the greater resistance of viruses and *Giardia* to disinfection. A new approach was needed to ensure the microbial safety of drinking water.

To achieve this goal a new treatment approach was developed called the Surface Treatment Rule (STR). As part of the STR, all water utilities that used surface waters as their source of potable water would be required to provide filtration to remove *Giardia* and enough disinfection to kill viruses. The problem facing the EPA was how much removal should be required. To deal with this issue, the EPA for the first time used a microbial risk assessment approach. The STR established that the goal of treatment was to ensure that microbial illness from *Giardia lamblia* infection should not be any greater than 1 per 10,000 exposed persons annually (10^{-4} per year). This value is close to the annual risk of infection from waterborne disease outbreaks in the United States (4×10^{-3}). Based on the estimated concentration of *Giardia* and enteric viruses in surface waters in the United States from the data available at the time, it was required that all drinking water treatment plants be capable of removing 99.9% of the *Giardia* and 99.99% of the viruses. In this manner it was hoped that the risk of infection of 10^{-4} per year would be achieved. The STR went into effect in 1991.

To better assess whether the degree of treatment required is adequate, the EPA developed the Information Collection Rule, which requires major drinking water utilities that serve surface waters to the public to analyze these surface waters for the presence of *Giardia, Cryptosporidium*, and enteric viruses for a period of almost 2 years. Utilities that have heavily contaminated source water may require greater levels of treatment in the future (see Fig. 24.5).

12. Using the exposure data in Example Calculation 24.1 determine the risk of infection and disease from *Salmonella* from a yearly exposure from lettuce.

13. If the concentration of *Cryptosporidium* oocysts in a stream is one oocyst per liter, how many $\log_{10}$ removals would you need to reduce the risk to 1:10,000, of becoming infected in a year, assuming two liters of drinking water are ingested per day? What treatment methods in series would you need to achieve this level of removal (see Chapter 27)?

14. What has a lower greater infectivity rotavirus or *Salmonella*?

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