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CHAPTER 4

Risk Assessmen

All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy. —Paracelsus (1493–1541)

4.1 INTRODUCTION

One of the most important changes in environmental policy in the 1980s was the acceptance of the role of risk assessment and risk management in environmental decision making. In early environmental legislation, such as the Clean Air and Clean Water Acts, the concept of risk is hardly mentioned; instead, these acts required that pollution standards be set that would allow adequate margins of safety to protect public health. Intrinsic to these standards was the assumption that pollutants have thresholds, and that exposure to concentrations below these thresholds would produce no harm. All of that changed when the problems of toxic waste were finally recognized and addressed. Many toxic substances are suspected carcinogens; that is, they may cause cancer, and for carcinogens the usual assumption is that even the smallest exposure creates some risk.

If any exposure to a substance causes some risk, how can air quality and water quality standards be set? When cleaning up a hazardous waste site, at what point is the project completed; that is, how clean is clean? At some point in the cleanup, the remaining health and environmental risks may not justify the continued costs and, from a risk perspective, society might be better off spending the money elsewhere. Almost by definition, achieving zero risk would cost an infinite amount of money, so policy makers have had to grapple with the tradeoff between acceptable risk and

acceptable cost. Complicating those decisions is our very limited understanding of diseases such as cancer coupled with a paucity of data on the tens of thousands of synthetic chemicals that are in widespread use today. Unfortunately, those who have responsibility for creating and administering environmental regulations have to take action even if definitive answers from the scientific community on the relationship between exposure and risk are not available.

The result has been the emergence of the controversial field of environmental risk assessment. Hardly anyone is comfortable with it. Scientists often deplore the notion of condensing masses of frequently conflicting, highly uncertain, often ambiguous data that have been extrapolated well beyond anything actually measured down to a single number or two. Regulatory officials are battered by the public when they propose a level of risk that they think a community living next to a toxic waste site should tolerate. Critics of government spending think risks are being systematically overestimated, resulting in too much money being spent for too little real improvement in public health. Others think risks are underestimated since risk assessments are based on data obtained for exposure to individual chemicals, ignoring the synergistic effects that are likely to occur when we are exposed to thousands of them in our daily lives.

Some of the aforementioned conflicts can best be dealt with if we make the distinction between risk assessment and risk management. *Risk assessment* is the scientific side of the story. It is the gathering of data that are used to relate response to dose. Such dose-response data can then be combined with estimates of likely human exposure to produce overall assessments of risk. *Risk management,* on the other hand, is the process of deciding what to do. It is decision making, under extreme uncertainty, about how to allocate national resources to protect public health and the environment. Enormous political and social judgment is required to make those decisions. Is a one-in-a-million lifetime risk of getting cancer acceptable and, if it is, how do we go about trying to achieve it?

4.2 PERSPECTIVES ON RISKS

The usual starting point for an explanation of risk is to point out that there is some risk in everything we do, and since we will all die someday, our lifetime risk of death from all causes is 1.0, or 100 percent. It is easy to gather good data on the causes of death, such as are shown in Table 4.1, which gives us one approach to talking about risk. For example, of the total 2.177 million deaths in the United States in 1992, there were roughly 521 thousand cancer deaths. Neglecting age structure complications, we could say that, on the average, the risk, or probability, of an American dying of cancer is therefore about 24 percent (521,000/2,177,000 = 0.24).

Notice that there are no units associated with risk, although other clarifiers may be needed, such as whether the risk is a lifetime risk or an annual risk, whether it is an average risk to the general public or a risk faced by individuals who engage in some activity, or whether it is being expressed as a percentage or as a decimal fraction. For example, in the United States, smoking is thought to be causing approximately 400,000 deaths per year. On the average, the probability of death caused by smoking is therefore about 18 percent (400,000/2,177,000 = 0.18). Obviously, however, the risk that an individual faces from smoking depends on how much that person smokes and how much exposure is caused by smoke from other people's cigarettes. The probability that a pack-a-day smoker will die of lung cancer, heart disease, or emphysema brought on by smoking is about 0.25, or 25 percent (Wilson and Crouch, 1987). Statistically, smokers shorten their life expectancy by about 5 minutes for each cigarette smoked, which is roughly the time it takes to smoke that cigarette.

TABLE 4.1 Leading Causes of Death in the United States, 1992

Cause	Annual deaths (thousands)	Percent
Cardiovascular (heart) disease	720	33
Cancer (malignant neoplasms)	521	24
Cerebrovascular diseases (strokes)	144	7
Pulmonary diseases (bronchitis, emphysema, asthma)	91	4
Pneumonia and influenza	76	3
Diabetes mellitus	50	2
Non-motor-vehicle accidents	48	2
Motor vehicle accidents	42	2
HIV/AIDS	34	1.6
Suicides	30	1.4
Homicides	27	1.2
All other causes	394	18
Total annual deaths (rounded)	2177	100

Source: Kolluru (1996).

Environmental risk assessments deal with incremental probabilities of some harm occurring. For example, the Environmental Protection Agency (EPA) attempts to control our exposure to toxics to levels that will pose incremental lifetime cancer risks to the most exposed members of the public of roughly 10^{-6} (one additional cancer in one million people) to 10^{-4} (100 additional cancers per million people). For perspective, suppose all 260 million Americans faced a 10^{-6} lifetime risk of cancer from exposure to a particular toxic chemical. That would mean 260 extra cancers during their lifetimes. Suppose we assume a typical lifetime of 70 years. Then spreading those 260 cancers out over 70 years suggests roughly four extra cancers per year in the United States. Table 4.1 tells us there are 521,000 cancer deaths per year, so the four extra cancers caused by toxic exposure would be less than 0.001 percent of the nominal rate.

Presenting risks as an annual probability of death to individuals who engage in some activity is a much more specific way to express risks than simply looking at the population as a whole. Table 4.2 shows risk data for some common activities. For example, the probability of dying in a motorcycle accident among those who ride motorcycles is 2000 deaths per year per 100,000 motorcyclists. Another example is the risk associated with consuming 4 tablespoons of peanut butter per day. It turns out that mold on peanuts creates a group of chemicals called *aflatoxins* that are known to cause malignant tumors in a number of animals, such as rats, mice, guinea pigs, and monkeys. The Food and Drug Administration (FDA) restricts the aflatoxin concentration in peanut products to 20 ppb (a risk-based decision), and at that level, eating 4 tablespoons of peanut butter per day may cause an estimated 0.8 cancer deaths per year per

TABLE 4.2 Annual risks of death associated with certain activities.

Activity/exposure	Annual risk (Deaths per 100,000 persons at risk)
Motorcycling	2000
Smoking, all causes	300
Smoking (cancer)	120
Hang gliding	80
Coal mining	63
Farming	36
Motor vehicles	24
Chlorinated drinking water (chloroform)	0.8
4 tbsp peanut butter per day (aflatoxin)	0.8
3 oz charcoal broiled steak per day (PAHs)	0.5
1-in-a-million lifetime risk	0.0014

Source: Based on Wilson and Crouch, 1987.

100,000. Another interesting item on the list is associated with the polycyclic aromatic hydrocarbons (PAHs) created when food is charbroiled. As will be described in Chapter 7, PAHs are formed when carbon-containing materials are not completely oxidized during combustion, so consumption of burned steak poses some cancer risk. In Table 4.2 that risk is estimated at 0.5 deaths per year per 100,000 people who eat 3 ounces of broiled steak per day. Notice, for comparison, that the annual risk associated with a "one-in-a-million" lifetime risk is about 0.0014 per 100,000.

The data in Table 4.1 are based on actuarial data, so they may be considered accurate, but the data in Tables 4.2 and 4.3 are a mix of actuarial values and estimates based on various risk models. It should be always be kept in mind that when risks are based on models, there are generally very large uncertainties in the estimates.

Wilson (1979) provides some perspectives on risk by comparing various activities on the basis of equal, one-in-one-million (10^{-6}) risks. For example, aircraft statistics indicate that 100 billion passenger miles of travel each year in the United States result in about 100 deaths per year; that is, one death per billion passenger miles. A trip of 1000 miles would therefore result in a risk of about 10^{-6}. As another example, Wilson cites statistics on death rates caused by sulfur emissions from coal plants east of the Mississippi. At 20,000 deaths per year among 100 million people exposed to this dirty air, the average risk would be 20,000/100,000,000, or 0.0002 per year of exposure. Two days of breathing this polluted air would pose a risk of $2/365 \times 0.0002 = 10^{-6}$. Other examples of one-in-one-million risks are given in Table 4.3. As suggested there, for example, smoking 1.4 cigarettes is equivalent in risk terms to living 50 years within 5 miles of a nuclear power plant. Again, bear in mind that these values are at best rough approximations.

One of the purposes of risk assessment is to provide a starting point in balancing the tradeoffs between an acceptable incremental risk and the cost of controlling risk to that level. Table 4.4 shows some estimated expenditures to prevent a life from being shortened by one year. Immunizations and phasing out leaded gasoline are indicated to have no cost to them because the direct savings in health care far exceed their cost.

TABLE 4.3 Activities that increase mortality risk by one in a million

Activity	Type of risk
Smoking 1.4 cigarettes	Cancer, heart disease
Drinking 1/2 liter of wine	Cirrhosis of the liver
Spending 1 hour in a coal mine	Black lung disease
Living 2 days in New York or Boston	Air pollution
Traveling 300 miles by car	Accident
Flying 1000 miles by jet	Accident
Flying 6000 miles by jet	Cancer by cosmic radiation
Traveling 10 miles by bicycle	Accident
Traveling 6 minutes by canoe	Accident
Living 2 summer months in Denver (vs. sea level)	Cancer by cosmic radiation
Living 2 months with a cigarette smoker	Cancer, heart disease
Eating 40 tablespoons of peanut butter	Liver cancer caused by aflatoxin
Eating 100 charcoal-broiled steaks	Cancer from benzopyrene
Living 50 years within 5 miles of a nuclear reactor	Accident releasing radiation

Source: Wilson (1979).

TABLE 4.4 Estimated expenditures per life-year saved for selected programs

Program	1990 U.S. $
Childhood immunizations	Direct savings
Eliminating lead in gasoline	Direct savings
Safety rules at underground construction sites	52,000
Hemodialysis at a dialysis center	56,000
Coronary artery bypass surgery	68,000
Front seat air bags in new cars	109,000
Dioxin effluent controls at paper mills	5,570,000

Source: Kolluru (1996) based on data from the Harvard School of Public Health.

Pollution control in the case of lead emissions is very cost-effective, but the table suggests that saving lives by controlling dioxin at a paper mill is very costly indeed.

4.3 PERCEPTION OF RISK

Data such as those given in the preceding tables are often used to try to put the health risk associated with pollution into perspective. It usually turns out, however, that the perceptions of risk as seen by an engineer or scientist familiar with the numbers are very different from those of an individual who lives next to a toxic waste site. Social scientists have studied this phenomenon and conclude that there are a number of attributes of risk that can increase the anxiety level of someone evaluating his or her own personal exposures.

For example, people are more likely to be outraged when they have no control of the risks they are exposed to, and they are more fearful of unknown risks than ones they are familiar with. We quite readily take on the risk of crashing into a tree when skiing, because it is a voluntary activity and we are familiar with and understand the risks. We put ourselves at great risk by driving cars, but we feel somewhat in control and believe the risk is worth the benefits. We also accept natural risks such as earthquakes and hurricanes much more readily than unnatural ones, such as the 1984 explosion of a methyl isocyanate storage tank in Bhopal, India, which killed 3400 people. And we are probably more comfortable living next to a gas station, despite the exposure to the carcinogen benzene, than living anywhere near a nuclear power plant, with its perceived unknown and uncertain risks. Table 4.5 illustrates this notion by comparing attributes that seem to be associated with elevated perceptions of risk.

That these risk attributes can be so important to the public can be a source of frustration in the technical community, but they are real and must be acknowledged by anyone who needs to communicate risk concepts to the public. Finding a way to help people act on the real risks in life and worry less about the minor ones is a difficult challenge.

4.4 RISK ASSESSMENT

Our concern is with the probability that exposure of some number of people to some combination of chemicals will cause some amount of response, such as cancer, reproductive failure, neurological damage, developmental problems, or birth defects. That is, we want to begin to develop the notions of risk assessment. The National Academy of Sciences (1983) suggests that risk assessment be divided into the following four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. After a risk assessment has been completed, the important stage of risk management follows, as shown in Figure 4.1.

TABLE 4.5 Some characteristics that elevate the perception of risk.

Attributes that elevate the perception of risk	Attributes that lower perception
Involuntary	Voluntary
Exotic	Familiar
Uncontrollable	Controllable
Controlled by others	Controlled by self
Dread	Accept
Catastrophic	Chronic
Caused by humans	Natural
Inequitable	Equitable
Permanent effect	Temporary effect
No apparent benefits	Visible benefits
Unknown	Known
Uncertainty	Certainty
Untrusted source	Trusted source

Source: based on Slovic (1987) and Slovic et al. (1980).

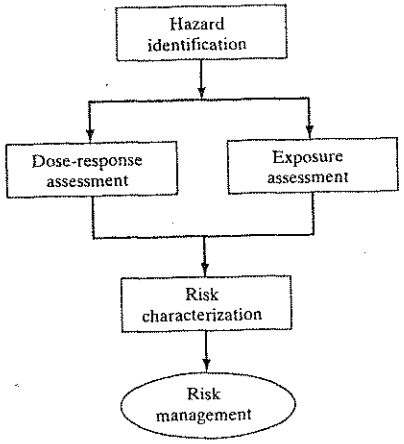

FIGURE 4.1 Risk assessment is usually considered to be a four-step process, followed by risk management.

- *Hazard identification* is the process of determining whether or not a particular chemical is causally linked to particular health effects, such as cancer or birth defects. Since human data are so often difficult to obtain, this step usually focuses on whether a chemical is toxic in animals or other test organisms.
- *Dose-response assessment* is the process of characterizing the relationship between the dose of an agent administered or received and the incidence of an adverse health effect. Many different dose-response relationships are possible for any given agent depending on such conditions as whether the response is carcinogenic (cancer causing) or noncarcinogenic and whether the experiment is a one-time acute test or a long-term chronic test. Since most tests are performed with high doses, the dose-response assessment must include a consideration for the proper method of extrapolating data to low exposure rates that humans are likely to experience. Part of the assessment must also include a method of extrapolating animal data to humans.
- *Exposure assessment* involves determining the size and nature of the population that has been exposed to the toxicant under consideration, and the length of time and toxicant concentration to which they have been exposed. Consideration must be given to such factors as the age and health of the exposed population, smoking history, the likelihood that members of the population might be pregnant, and whether or not synergistic effects might occur due to exposure to multiple toxicants.
- *Risk characterization* is the integration of the foregoing three steps, which results in an estimate of the magnitude of the public-health problem.

4.5 HAZARD IDENTIFICATION

The first step in a risk analysis is to determine whether or not the chemicals that a population has been exposed to are likely to have any adverse health effects. This is the work of toxicologists, who study both the nature of the adverse effects caused by toxic agents as well as the probability of their occurrence. We shall start our description of this hazard identification process by summarizing the pathways that a chemical may take as it passes through a human body and the kinds of damage that may result. A simple diagram of the human circulatory system is shown in Figure 4.2 that identifies some of the principal organs and the nomenclature for toxic effects.

A toxicant can enter the body using any of three pathways: by ingestion with food or drink, through inhalation, or by contact with the skin (dermal) or other exterior surfaces, such as the eyes. Once in the body it can be absorbed by the blood and distributed to various organs and systems. The toxicant may then be stored (for example, in fat, as in the case of DDT), or it may be eliminated from the body by excretion

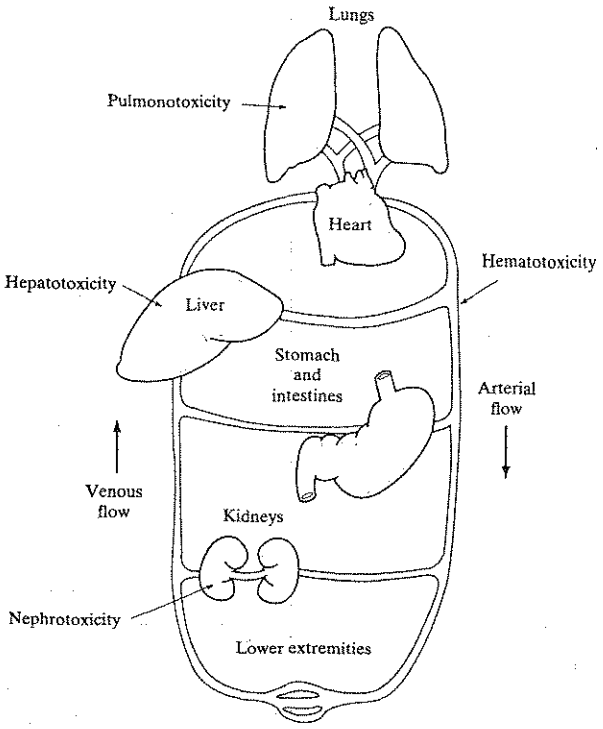

FIGURE 4.2 The circulatory system and nomenclature for toxic effects: hepatotoxicity (liver), nephrotoxicity (kidneys), pulmonotoxicity (lungs), hematotoxicity (blood). (*Source:* Based on James, 1985)

or by transformation into something else. The biotransformation process usually yields metabolites that can be more readily eliminated from the body than the original chemicals; however, metabolism can also convert chemicals to more toxic forms. Figure 4.3 presents the most important movements of chemical toxicants in the body, showing absorption, distribution, storage, and excretion. Although these are shown as separate operations, they all occur simultaneously.

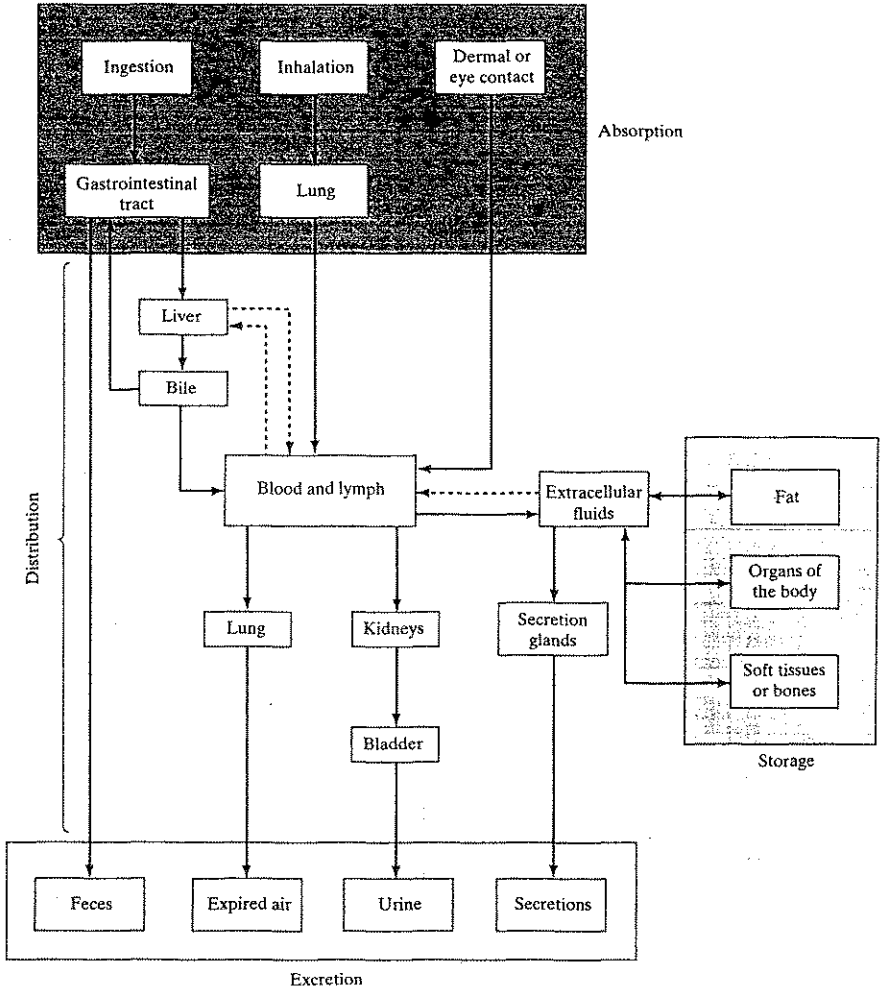

FIGURE 4.3 Fate of chemical toxicants in the body. (*Source:* Environ, 1988)

There are several organs that are especially vulnerable to toxicants. The liver, for example, which filters the blood before it is pumped through the lungs, is often the target. Since toxics are transported by the bloodstream, and since the liver is exposed to so much of the blood supply, it can be directly damaged by toxics. Moreover, since a major function of the liver is to metabolize substances, converting them into forms that can be excreted more easily from the body, it is also susceptible to chemical attack by toxic chemicals formed during the biotransformation process itself. Chemicals that can cause liver damage are called *hepatotoxins.* Examples of hepatotoxic agents include a number of synthetic organic compounds, such as carbon tetrachloride (CCl_4), chloroform ($CHCl_3$), and trichloroethylene (C_2HCl_3); pesticides, such as DDT and paraquat; heavy metals, such as arsenic, iron, and manganese; and drugs, such as acetaminophen and anabolic steroids. The kidneys also filter the blood, and they too are frequently susceptible to damage.

Toxic chemicals often injure other organs and organ systems as well. The function of the kidneys is to filter blood to remove wastes that will be excreted in the form of urine. Toxicants that damage the kidneys, called *nephrotoxics,* include metals such as cadmium, mercury, and lead, as well as a number of chlorinated hydrocarbons. Excessive kidney damage can decrease or stop the flow of urine, causing death by poisoning from the body's own waste products. *Hematotoxicity* is the term used to describe the toxic effects of substances on the blood. Some hematotoxins, such as carbon monoxide in polluted air and nitrates in groundwater, affect the ability of blood to transport oxygen to the tissues. Other toxicants, such as benzene, affect the formation of platelets, which are necessary for blood clotting. The lungs and skin, due to their proximity to pollutants, are also often affected by chemical toxicants. Lung function can be impaired by such substances as cigarette smoke, ozone, asbestos, and quartz rock dust. The skin reacts in a variety of ways to chemical toxicants, but the most common and serious environmentally related skin problem is cancer induced by excessive ultraviolet radiation, as will be described in Chapter 8.

Acute Toxicity

This chapter began with a quote by Philippus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus to the effect that it is the dose that makes the poison. One measure of the toxicity of something is the amount needed to cause some acute response, such as organ injury, coma, or even death. Acute toxicity refers to effects that are caused within a short period of time after a single exposure to the chemical; later we will discuss chronic toxicity effects that take place after prolonged exposure periods.

One way to describe the toxicity of chemicals is by the amount that is required to kill the organism. Table 4.6 shows a conventional toxicity rating scheme that expresses the dose in terms of milligrams of chemical ingested per kilogram of body weight. That is, ingestion of a given amount of toxin will be more dangerous for a small person, such as a child, than a larger adult. Normalizing the dose using body weight is the first step in trying to relate a lethal dose to a laboratory animal to what might be expected in a human. For example, it takes on the order of 20,000 mg of ordinary sucrose per kilogram to kill a rat. Using the rating system in Table 4.6, sucrose would be considered

TABLE 4.6 A conventional rating system for the acute toxicity of chemicals in humans

	Probable lethal oral dose for humans	
Toxicity rating	Dose (mg/kg of body weight)	For average adult
1. Practically nontoxic	more than 15,000	More than 1 quart
2. Slightly toxic	5,000–15,000	1 pint to 1 quart
3. Moderately toxic	500–5,000	1 ounce to 1 pint
4. Very toxic	50–500	1 teaspoon to 1 ounce
5. Extremely toxic	5–50	7 drops to 1 teaspoon
6. Supertoxic	Less than 5	Less than 7 drops

practically nontoxic. If we scale up that dose to a 70-kg human (without any other adjustments), it might take something like 1.4 kg of sucrose (3 pounds) ingested all at one time to be lethal. At the other extreme, the bacteria *Clostridium botulinum* responsible for botulism (food poisoning), is lethal with a single dose of only 0.00001 mg/kg, so it is supertoxic (Rodricks, 1992).

Not every member of an exposed population will react the same way to a toxin, so one way to illustrate the variation is with a dose-response curve that shows the percentage of a population that is affected as a function of the dose received. In the dose-response curves of Figure 4.4, a logarithmic scale for dose is shown, which tends to yield the familiar S-shaped curve. Also notice that the dose is expressed as milligram of chemical ingested per kilogram of body weight. Normalizing with body weight allows the dose to be extrapolated to individuals of different sizes, such as a child versus an adult. Also, it provides a first cut at extrapolating the likely effects on a human when the dose-response curve has been generated using animal tests.

The curves of Figure 4.4 show the response to chemical exposure as a mortality rate. The dose that will kill 50 percent of a population is designated LD_{50}, where LD stands for lethal dose. In Figure 4.4*a*, the dose-response curves for two chemicals are shown. Chemical A has a lower LD_{50} than Chemical B and it is always more toxic. Figure 4.4b warns us to be aware that just because one chemical has a lower LD_{50} than

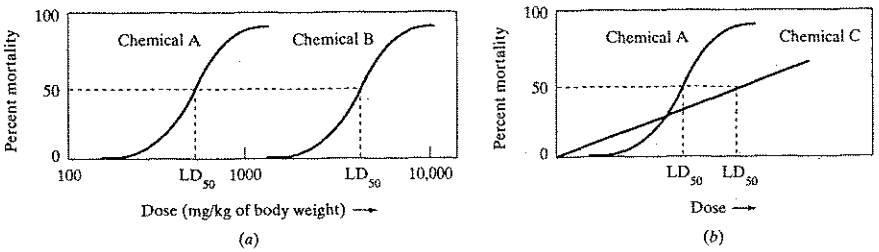

FIGURE 4.4 Dose-response mortality curves for acute toxicity: (a) Chemical A is always more toxic than B; (b) but Chemical A is less toxic than C at low doses even though it has a lower LD_{50}.

another does not necessarily mean it is always more toxic. Chemical A has a lower LD_{50}, which would normally suggest it is more toxic than C, but notice it is not as toxic as C at low doses. So the dose-response curve does provide more information than a simple table of LD_{50} doses.

Mutagenesis

In contrast to the short-term responses associated with acute toxicity, most risk assessments are focused on responses that may take years to develop. Measuring the ability of specific chemicals to cause cancer, reproductive failure, and birth defects is much more difficult than the acute toxicity testing just described.

Deoxyribonucleic acid (DNA) is an essential component of all living things and a basic material in the chromosomes of the cell nucleus. It contains the genetic code that determines the overall character and appearance of every organism. Each molecule of DNA has the ability to replicate itself exactly, transmitting that genetic information to new cells. Our interest here in DNA results from the fact that certain chemical agents, as well as ionizing radiation, are *genotoxic;* that is, they are capable of altering DNA. Such changes, or *mutations,* in the genetic material of an organism can cause cells to misfunction, leading in some cases to cell death, cancer, reproductive failure, or abnormal offspring. Chemicals that are capable of causing cancer are called *carcinogens;* chemicals that can cause birth defects are *teratogens.*

Mutations may affect somatic cells, which are the cells that make up the tissues and organs of the body itself, or they may cause changes in germ cells (sperm or ovum) that may be transmitted to future offspring. As is suggested in Figure 4.5, one possible outcome of a mutagenic event is the death of the cell itself. If the mutation is in a somatic cell and it survives, the change may be such that the cell no longer responds to signals that normally control cell reproduction. If that occurs, the cell may undergo rapid and uncontrolled cellular division, forming a tumor. Mutations in somatic cells may damage or kill the affected individual, and if the individual is a pregnant female, the embryo may be damaged, leading to a birth defect. Germ cell mutations, on the other hand, have the potential to become established in the gene pool and be transmitted to future generations.

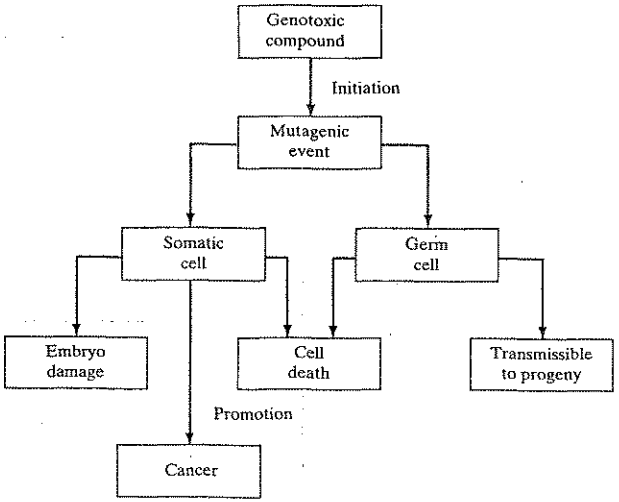

FIGURE 4.5 Possible consequences of a mutagenic event in somatic and germinal cells.

Carcinogenesis

Cancer is second only to heart disease in terms of the number of Americans killed every year. Every year close to 1 million people are diagnosed with cancer, and over one-half million die each year. Cancer is truly one of the most dreaded diseases.

Chemically induced carcinogenesis is thought to involve two distinct stages, referred to as *initiation* and *promotion.* In the initiation stage, a mutation alters a cell's genetic material in a way that may or may not result in the uncontrolled growth of cells that characterizes cancer. In the second, or promotion, stage of development, affected cells no longer recognize growth constraints that normally apply and a tumor develops. Promoters can increase the incidence rate of tumors among cells that have already undergone initiation, or they can shorten the latency period between initiation and the full carcinogenic response. The model of initiation followed by promotion suggests that some carcinogens may be initiators, others may be promoters, and some may be complete carcinogens capable of causing both stages to occur. Current regulations do not make this distinction, however, and any substance capable of increasing the incidence of tumors is considered a carcinogen, subject to the same risk assessment techniques. Tumors, in turn, may be *benign* or *malignant* depending on whether or not the tumor is contained within its own boundaries. If a tumor undergoes *metastasis*—that is, it breaks apart and portions of it enter other areas of the body—it is said to be malignant. Once a tumor has metastasized, it is obviously much harder to treat or remove.

The theoretical possibility that a single genotoxic event can lead to a tumor is referred to as the *one-hit hypothesis.* Based on this hypothesis, exposure to even the smallest amount of a carcinogen leads to some nonzero probability that a malignancy will result. That is, in a conservative, worst-case risk assessment for carcinogens, it is assumed that there is no threshold dose below which the risk is zero.

A brief glossary of carcinogenesis terminology is presented in Table 4.7.

Toxicity Testing in Animals

With several thousand new chemicals coming onto the market each year, a backlog of tens of thousands of relatively untested chemicals already in commerce, and a limited number of facilities capable of providing the complex testing that might be desired, it is just not possible to test each and every chemical for its toxicity. As a result, a hierarchy of testing procedures has been developed that can be used to help select those chemicals that are most likely to pose serious risks.

The starting point is the relatively straightforward acute toxicity testing already described. The next step may be to compare the structure of the chemical in question with other chemicals that are known or suspected to be human carcinogens, such as

TABLE 4.7 Glossary of Carcinogenesis Terminology

Acute toxicity	Adverse effects caused by a toxic agent occurring within a short period of time following exposure
Benign tumor	A new tumor composed of cells that, though proliferating in an abnormal manner, do not spread to surrounding, normal tissue
Cancer	An abnormal process in which cells begin a phase of uncontrolled growth and spread
Carcinogen	Any cancer-producing substance
Carcinoma	A malignant tumor in the tissue that covers internal or external surfaces of the body such as the stomach, liver, or skin
Chronic toxicity	Adverse effects caused by a toxic agent after a long period of exposure
Initiator	A chemical that initiates the change in a cell that irreversibly converts the cell into a cancerous or precancerous state
Malignant tumor	Relatively autonomous growth of cells or tissue that invade surrounding tissue and have the ability to metastasize
Mutagenesis	Alteration of DNA in either somatic or germinal cells not associated with the normal process of recombination
Mutation	A permanent, transmissible change in DNA that changes the function or behavior of the cell
Neoplasm	Literally, new growth, usually of an abnormally fast-growing tissue
Oncogenic	Giving rise to tumors or causing tumor formation
Pharmacokinetics	The study of how a chemical is absorbed, distributed, metabolized, and excreted
Promoter	A chemical that can increase the incidence of response to a carcinogen previously administered
Sarcoma	A cancer that arises from mesodermal tissue (e.g., fat, muscle, bone)
Teratogen	Any substance capable of causing malformation during development of the fetus
Toxicity	A relative term generally used in comparing the harmful effect of one chemical on some biological mechanism with the effect of another chemical

Source: Based on Williams and Burson, 1985.

those shown in Figure 4.6. New chemicals that are similar to these, and other suspected carcinogens, would be potential candidates for further testing.

The prevailing carcinogenesis theory, that human cancers are initiated by gene mutations, has led to the development of short-term, in vitro (in glassware) screening procedures, which are one of the first steps taken to determine whether a chemical is carcinogenic. It is thought that if a chemical can be shown to be mutagenic, then it *may* be carcinogenic, and further testing may be called for. The most widely used short-term test, called the *Ames mutagenicity assay,* subjects special tester strains of bacteria to the chemical in question. These tester strains have previously been rendered incapable of normal bacterial division so, unless they mutate back to a form that is capable of division, they will die. Bacteria that survive and form colonies do so through mutation; therefore, the greater the survival rate of these special bacteria, the more mutagenic is the chemical.

Intermediate testing procedures involve relatively short-term (several months duration) carcinogenesis bioassays in which specific organs in mice and rats are subjected to known mutagens to determine whether tumors develop.

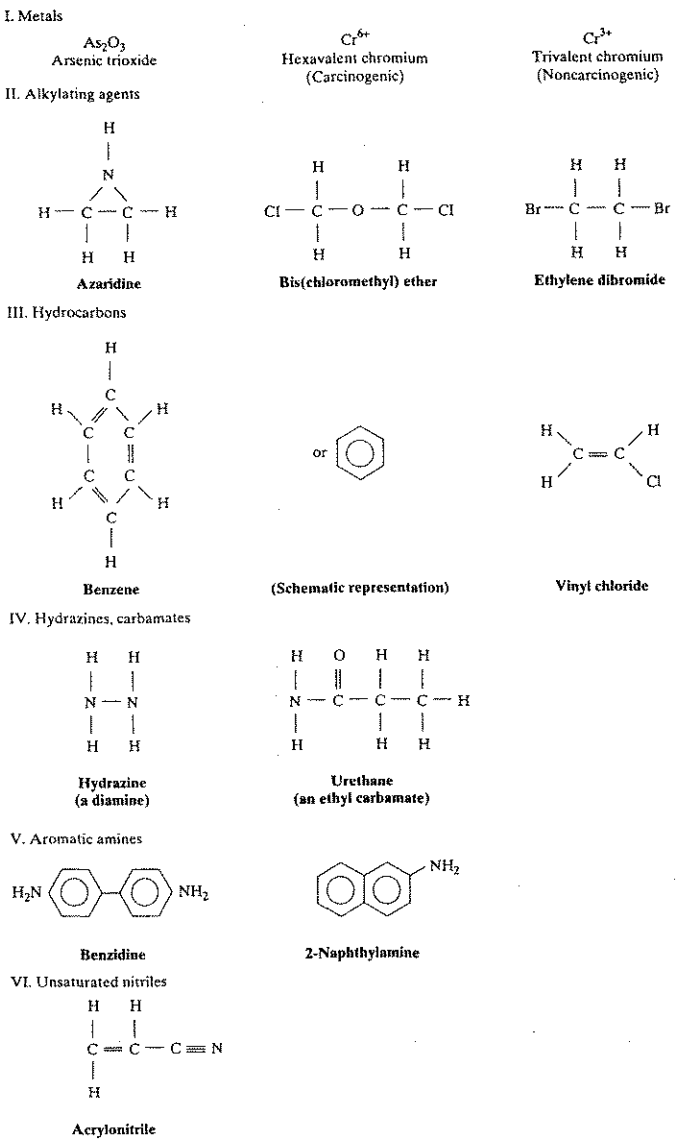

FIGURE 4.6 Selected structural formulae for some classes of carcinogenic chemicals. (Williams and Burson, 1985)

Finally, the most costly, complex, and long-lasting test, called a *chronic carcinogenesis bioassay,* involves hundreds or thousands of animals over a time period of several years. To assure comparable test results and verifiable data, the National Toxicology Program in the United States has established minimum test requirements for an acceptable chronic bioassay, which include the following:

- *Two species of rodents must be tested.* Mice and rats, using specially inbred strains for consistency, are most often used. They have relatively short lifetimes, and their small size makes them easier to test in large numbers.
- *At least 50 males and 50 females of each species for each dose must be tested.* Many more animals are required if the test is to be sensitive enough to detect risks of less than a few percent.
- *At least two doses must be administered (plus a no-dose control).* One dose is traditionally set at the maximum tolerated dose (MTD), a level that can be administered for a major portion of an animal's lifetime without significantly impairing growth or shortening the lifetime. The second dose is usually one-half or one-fourth the MTD.

Exposure begins at 6 weeks of age and ends when the animal reaches 24 months of age. At the end of the test, all animals are killed and their remains are subjected to detailed pathological examinations. These tests are expensive as well as time consuming. Testing a typical new chemical costs between $500,000 and $1.5 million, takes up to two or three years, and may entail the sacrifice of thousands of animals (Goldberg and Frazier, 1989).

Notice that, following the aforementioned protocol, the minimum number of animals required for a bioassay is 600 (2 species × 100 animals × 3 doses), and at that number it is still only relatively high risks that can be detected. With this number of animals, for the test to show a statistically significant effect, the exposed animals must have at least 5 or 10 percent more tumors than the controls in order to conclude that the extra tumors were caused by the chemical being tested. That is, the risk associated with this chemical can be measured only down to roughly 0.05 or 0.10 unless we test a lot more animals.

A simple example may help to clarify this statistical phenomenon. Suppose we test 100 rats at a particular dose and find one tumor. To keep it easy, let's say the control group never gets tumors. Can the actual probability (risk) of tumors caused by this chemical at this dose be 1 percent? Yes, definitely. If the risk is 1 percent we would expect to get one tumor, and that is what we got. Could the actual probability be 2 percent? Well, if the actual risk is 2 percent, and *if we were able to run the test over and over again* on sets of 100 rats each, some of those groups would have no tumors, some would certainly have one tumor, and some would have more. So our actual test of only one group of 100, which found one tumor, is not at all inconsistent with an actual risk of 2 percent. Could the actual risk be 3 percent? Running many sets of 100 rats through the test would likely result in at least one of those groups having only one tumor. So it would not be out of the question to find one tumor in a single group of 100 rats even if the actual risk is 3 percent. Getting back to the original test of 100 rats and finding one tumor, we have just argued that the actual risk could be anything from 0 percent to, say,

2 or 3 percent, maybe even more, and still be consistent with finding just one tumor. We certainly cannot conclude that the risk is only 1 percent. In other words, with 100 animals we cannot perform a statistically significant test and be justified in concluding that the risk is anything less than a few percent. Bioassays designed to detect lower risks require many thousands of animals. In fact, the largest experiment ever performed involved over 24,000 mice and yet was still insufficiently sensitive to measure a risk of less than 1 percent (Environ, 1988).

The inability of a bioassay to detect small risks presents one of the greatest difficulties in applying the data so obtained to human risk assessment. Regulators try to restrict human risks due to exposure to carcinogens to levels of about 10^{-6} (one in a million), yet animal studies are only capable of detecting risks of down to 0.01 to 0.1. It is necessary, therefore, to find some way to extrapolate the data taken for animals exposed to high doses to humans who will be exposed to doses that are several orders of magnitude lower.

Human Studies

Another shortcoming in the animal testing methods just described, besides the necessity to extrapolate the data toward zero risk, is the obvious difficulty in interpreting the data for humans. How does the fact that some substance causes tumors in mice relate to the likelihood that it will cause cancer in humans as well? Animal testing can always be criticized in this way, but since we are not inclined to perform the same sorts of tests directly on humans, other methods must be used to gather evidence of human toxicity.

Sometimes human data can be obtained by studying victims of tragedies, such as the chemical plant explosion that killed and injured thousands in Bhopal, India, and the atomic bombing of Hiroshima and Nagasaki, Japan. The most important source of human risk information, however, comes from epidemiologic studies. Epidemiology is the study of the incidence rate of diseases in real populations. By attempting to find correlations between disease rates and various environmental factors, an epidemiologist attempts to show in a quantitative way the relationship between exposure and risk. Such data can be used to complement animal data, clinical data, and scientific analyses of the characteristics of the substances in question.

Epidemiologists have a number of strategies for gathering useful information, but they share the common feature of trying to identify two populations of people having different exposures to the risk factor being studied. Preliminary data analysis usually involves setting up a simple 2 × 2 matrix such as the one shown in Figure 4.7. The rows divide the populations according to those who have, and those who have not,

	With disease	Without disease
Exposed	*a*	*b*
Not exposed	*c*	*d*

FIGURE 4.7 A 2 × 2 matrix for an epidemiologic rate comparison. Rows divide people by exposure; columns divide them by disease.

been exposed to the risk factor. The columns are based on the numbers of individuals who have acquired the disease being studied and those who have not.

Various measures can be applied to the data given in Figure 4.7 to see whether they *suggest* an association between exposure and disease.

- The *relative risk* is defined as

$$\text{Relative risk} = \frac{a/(a+b)}{c/(c+d)} \tag{4.1}$$

Notice that the numerator is the fraction of those exposed who have the disease, and the denominator is the fraction of those exposed who ~~do not~~ not have the disease. If those two ratios are the same, the odds of having the disease would not depend on whether an individual had been exposed to the risk factor, and the relative risk would be 1.0. Above 1.0, the higher the relative risk the more the data suggests an association between exposure and risk.

- The *attributable risk* is defined as

$$\text{Attributable risk} = \frac{a}{a+b} - \frac{c}{c+d} \tag{4.2}$$

The attributable risk is the difference between the odds of having the disease with exposure and the odds of having the disease without exposure. An attributable risk of 0.0 suggests no relationship between exposure and risk.

- The *odds ratio* is defined as the cross product of the entries in the matrix:

$$\text{Odds ratio} = \frac{ad}{bc} \tag{4.3}$$

The odds ratio is similar to the relative risk. Numbers above 1.0 suggest a relationship between exposure and risk.

EXAMPLE 4.1 Epidemiologic Data Analysis

An evaluation of personnel records for employees of a plant that manufactures vinyl chloride finds that out of 200 workers, 15 developed liver cancer. A control group consisting of individuals with smoking histories similar to the exposed workers, and who were unlikely to have encountered vinyl chloride, had 24 with liver cancers and 450 who did not develop liver cancer. Find the relative risk, attributable risk, and odds ratio for these data.

Solution Putting the data into the 2 x 2 matrix gives

	D	$\overline{D}$
E	15	185
$\overline{E}$	24	450

Solving for each measure yields:

$$\text{Relative risk} = \frac{15/(15+185)}{24/(24+450)} = \frac{.075}{0.05} = 1.48$$

$$\text{Attributable risk} = \frac{15}{200} - \frac{24}{474} = 0.024$$

$$\text{Odds ratio} = \frac{15 \times 450}{185 \times 24} = 1.52$$

The relative risk and the odds ratio both are above 1.0, so they suggest a relationship between exposure and risk. For those who were exposed, the risk of cancer has increased by 0.024 (the attributable risk) over that of their cohorts who were not exposed. All three measures indicate that further study of the relationship between vinyl chloride and liver cancer would be warranted. ■

Caution must be exercised in interpreting every epidemiologic study since any number of confounding variables may lead to invalid conclusions. For example, the study may be biased because workers are compared with nonworkers (workers are generally healthier), or because relative rates of smoking have not been accounted for, or there may be other variables that are not even hypothesized in the study that may be the actual causal agent. As an example of the latter, consider an attempt to compare lung cancer rates in a city having high ambient air pollution levels with rates in a city having less pollution. Suppose the rates are higher in the more polluted city, even after accounting for smoking history, age distribution, and working background. To conclude that ambient air pollution is causing those differences may be totally invalid. Instead, it might well be different levels of radon in homes, or differences in other indoor air pollutants associated with the type of fuel used for cooking and heating, that are causing the cancer variations.

Weight-of-Evidence Categories for Potential Carcinogens

Based on the accumulated evidence from clinical studies, epidemiologic evidence, in vitro studies, and animal data, the EPA uses the following categories to describe the likelihood that a chemical substance is carcinogenic (U.S. EPA, 1986a). Using both human and animal data, five categories, A through E, have been established as follows:

Group A: Human carcinogen. A substance is put into this category only when there is sufficient epidemiologic evidence to support a causal association between exposure to the agent and cancer.

Group B: Probable human carcinogen. This group is actually made up of two subgroups. An agent is categorized as B1 if there is limited epidemiologic evidence; and it is put into B2 if there is inadequate human data but sufficient evidence of carcinogenicity in animals.

Group C: Possible human carcinogen. This group is used for agents with limited evidence of carcinogenicity in animals and an absence of human data.

Group D: Not classified. This group is for agents with inadequate human and animal evidence or for which no data are available.

Group E: Evidence of noncarcinogenicity. This group is used for agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

Table 4.8 summarizes this categorization scheme.

START: READING FOR LECTURE 3.

4.6 DOSE-RESPONSE ASSESSMENT

As the name suggests, the fundamental goal of a dose-response assessment is to obtain a mathematical relationship between the amount of a toxicant that a human is exposed to and the risk that there will be an unhealthy response to that dose. We have seen dose-response curves for acute toxicity, in which the dose is measured in milligram per kilogram of body weight. The dose-response curves that we are interested in here are the result of chronic toxicity; that is, the organism is subjected to a prolonged exposure over a considerable fraction of its life. For these curves the abscissa is dose, which is usually expressed as the average milligrams of substance per kilogram of body weight per day (mg/kg-day). The dose is an exposure averaged over an entire lifetime (for humans, assumed to be 70 years). The ordinate is the response, which is the risk that there will be some adverse health effect. As usual, response (risk) has no units; it is a probability that there will be some adverse health effect. For example, if prolonged exposure to some chemical would be expected to produce 700 cancers in a population of 1 million, the response could be expressed as 0.0007, 7×10^{-4}, or 0.07 percent. The annual risk would be obtained by spreading that risk over an assumed 70-year lifetime, giving a risk of 0.00001 or 1×10^{-5} per year.

For substances that induce a carcinogenic response, it is always conventional practice to assume that exposure to any amount of the carcinogen will create some likelihood of cancer. That is, a plot of response versus dose is required to go through the origin. For noncarcinogenic responses, it is usually assumed that there is some

TABLE 4.8 Weight-of-Evidence Categories for Human Carcinogenicity

	Animal Evidence				
Human Evidence	Sufficient	Limited	Inadequate	No Data	No Evidence
Sufficient	A	A	A	A	A
Limited	B1	B1	B1	B1	B1
Inadequate	B2	C	D	D	D
No data	B2	C	D	D	E
No evidence	B2	C	D	D	E

Source: USEPA (1986a).

threshold dose, below which there will be no response. As a result of these two assumptions, the dose-response curves and the methods used to apply them are quite different for carcinogenic and noncarcinogenic effects, as suggested in Figure 4.8. The same chemical, by the way, may be capable of causing both kinds of response.

To apply dose-response data obtained from animal bioassays to humans, a *scaling factor* must be introduced. Sometimes the scaling factor is based on the assumption that doses are equivalent if the dose per unit of body weight in the animal and human is the same. Sometimes, especially if the exposure is dermal, equivalent doses are normalized to body surface area rather than body weight when scaling up from animal to human. In either case, the resulting human dose-response curve is specified with the standard mg/kg-day units for dose. Adjustments between animal response and human response may also have to be made to account for differences in the rates of chemical absorption. If enough is known about the differences between the absorption rates in test animals and in humans for the particular substance in question, it is possible to account for those differences later in the risk assessment. Usually, though, there is insufficient data and it is simply assumed that the absorption rates are the same.

Extrapolations from High Doses to Low Doses

The most controversial aspect of dose-response curves for carcinogens is the method chosen to extrapolate from the high doses actually administered to test animals to the low doses to which humans are likely to be exposed. Recall that even with extremely large numbers of animals in a bioassay, the lowest risks that can be measured are usually a few percent. Since regulators attempt to control human risk to several orders of magnitude less than that, there will be no actual animal data anywhere near the range of most interest.

Many mathematical models have been proposed for the extrapolation to low doses. Unfortunately, no model can be proved or disproved from the data, so there is no way to know which model is the most accurate. That means the choice of models is strictly a policy decision. One commonly used model is called the *one-hit model,* in

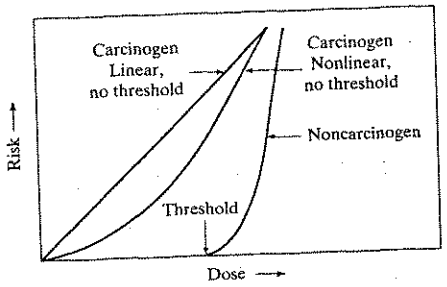

FIGURE 4.8 Dose-response curves for carcinogens are assumed to have no threshold; that is, any exposure produces some chance of causing cancer.

which the relationship between dose (d) and lifetime risk (probability) of cancer, $P(d)$, is given in the following form (Crump, 1984):

$$P(d) = 1 - e^{-(q_0 + q_1 d)} \tag{4.4}$$

where q_0 and q_1 are parameters picked to fit the data. The one-hit model corresponds to the simplest mechanistic model of carcinogenesis, in which it is assumed that a single chemical hit is capable of inducing a tumor.

If we substitute $d = 0$ into (4.1), the result will be an expression for the background rate of cancer incidence, $P(0)$. Using the mathematical expansion for an exponential

$$e^x = 1 + x + \frac{x^2}{2!} + \cdots + \frac{x^n}{n!} \cong 1 + x \quad \text{(for small } x\text{)} \tag{4.5}$$

and assuming that the background cancer rate is small allows us to write

$$P(0) = 1 - e^{-q_0} \cong 1 - [1 + (-q_0)] = q_0 \tag{4.6}$$

That is, the background rate for cancer incidence corresponds to the parameter q_0. Using the exponential expansion again, the one-hit model suggests that the lifetime probability of cancer for small dose rates can be expressed as

$$P(d) \cong 1 - [1 - (q_0 + q_1 d)] = q_0 + q_1 d = P(0) + q_1 d \tag{4.7}$$

For low doses, the additional risk of cancer above the background rate would be

$$\text{Additional risk} = A(d) = P(d) - P(0) \tag{4.8}$$

Substituting (4.7) into (4.8) yields the following equation for the additional cancer risk incurred when the organism in question is exposed to a dose d:

$$\text{Additional risk} = A(d) \cong q_1 d \tag{4.9}$$

That is, the one-hit model predicts that for low doses the extra lifetime probability of cancer is linearly related to dose.

The one-hit model relating risk to dose is not the only one possible. Another mathematical model that has been proposed has its roots in the multistage model of tumor formation; that is, that tumors are the result of a sequence of biological events (Crump, 1984). The *multistage* model expresses the relationship between risk and dose as

$$P(d) = 1 - e^{-(q_0 + q_1 d + q_2 d^2 + \cdots q_n d^n)} \tag{4.10}$$

where the individual parameters q_i are positive constants picked to best fit the dose-response data. Again, it is easy to show that for small values of dose d, the multistage model also has the simplifying feature of producing a linear relationship between additional risk and dose. Figure 4.9 illustrates the use of a one-hit model and a multistage model to fit experimental data. The multistage model will always fit the data better since it includes the one-hit model as a special case.

Since the choice of an appropriate low-dose model is not based on experimental data, there is no model that can be proved to be more correct than another. To protect public health, EPA chooses to err on the side of safety and overemphasize risk. The EPA's model of choice is a modified multistage model, called the *linearized multistage model*. It is linear at low doses with the constant of proportionality picked in a way that the probability of overestimating the risk is 95 percent.

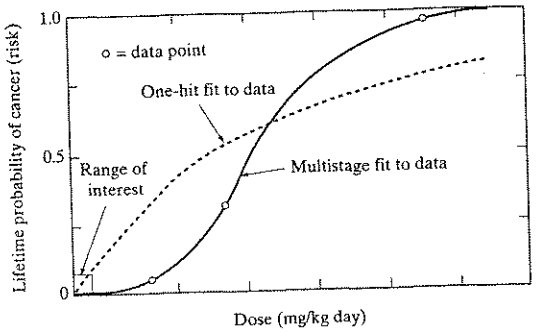

FIGURE 4.9 Dose-response curves showing two methods of fitting an equation to the data. The range of interest is well below the point where any data actually exist. (Based on Crump, 1984)

Potency Factor for Carcinogens

For chronic toxicity studies, a low dose is administered over a significant portion of the animal's lifetime. The resulting dose-response curve has the incremental risk of cancer (above the background rate) on the y-axis, and the lifetime average daily dose of toxicant along the x-axis. At low doses, where the dose-response curve is assumed to be linear, the slope of the dose-response curve is called the *potency factor* (PF), or *slope factor*.

$$\text{Potency factor} = \frac{\text{Incremental lifetime cancer risk}}{\text{Chronic daily intake (mg/kg-day)}} \tag{4.11}$$

The denominator in (4.11) is the dose averaged over an entire lifetime; it has units of average milligrams of toxicant absorbed per kilogram of body weight per day, which is usually written as (mg/kg-day) or (mg/kg/day). Since risk has no units, the units for potency factor are therefore $(\text{mg/kg-day})^{-1}$.

If we have a dose-response curve, we can find the potency factor from the slope. In fact, one interpretation of the potency factor is that it is the risk produced by a chronic daily intake of 1 mg/kg-day, as shown in Figure 4.10.

Rearranging (4.11) shows us where we are headed. If we know the chronic daily intake CDI (based on exposure data) and the potency factor (from EPA), we can find the lifetime, incremental cancer risk from

$$\text{Incremental lifetime cancer risk} = \text{CDI} \times \text{Potency factor} \tag{4.12}$$

The linearized multistage risk-response model assumptions built into (4.12) should make this value an upper-bound estimate of the actual risk. Moreover, (4.12) estimates the risk of getting cancer, which is not necessarily the same as the risk of dying of cancer, so it should be even more conservative as an upper-bound estimate of cancer death rates.

Potency factors needed for (4.12) can be found in an EPA database on toxic substances called the Integrated Risk Information System (IRIS). Included in the rather extensive background information on each potential carcinogen in IRIS is the potency factor and the weight-of-evidence category (recall Table 4.8). A short list of some of

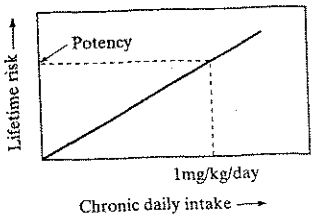

FIGURE 4.10 The potency factor is the slope of the dose-response curve. It can also be thought of as the risk that corresponds to a chronic daily intake of 1 mg/kg-day.

these chemicals, potency factors (for both oral and inhalation exposure routes), and cancer categories is given in Table 4.9.

The other factor we need to develop more fully in order to use the basic risk equation (4.12) is the concept of chronic daily intake. The CDI is, by definition,

$$\text{CDI (mg/kg-day)} = \frac{\text{Average daily dose (mg/day)}}{\text{Body weight (kg)}} \tag{4.13}$$

The numerator in (4.13) is the total lifetime dose averaged over an assumed 70-year lifetime. The next example shows how to combine CDI and potency to find risk.

TABLE 4.9 Toxicity data for selected potential carcinogens

Chemical	Category	Potency factor oral route $(\text{mg/kg-day})^{-1}$	Potency factor inhalation route $(\text{mg/kg-day})^{-1}$
Arsenic	A	1.75	50
Benzene	A	2.9×10^{-2}	2.9×10^{-2}
Benzol(a)pyrene	B2	11.5	6.11
Cadmium	B1	—	6.1
Carbon tetrachloride	B2	0.13	—
Chloroform	B2	6.1×10^{-3}	8.1×10^{-2}
Chromium VI	A	—	41
DDT	B2	0.34	—
1,1-Dichloroethylene	C	0.58	1.16
Dieldrin	B2	30	—
Heptachlor	B2	3.4	—
Hexachloroethane	C	1.4×10^{-2}	—
Methylene chloride	B2	7.5×10^{-3}	1.4×10^{-2}
Nickel and compounds	A	—	1.19
Polychlorinated biphenyls (PCBs)	B2	7.7	—
2,3,7,8-TCDD (dioxin)	B2	1.56×10^{5}	—
Tetrachloroethylene	B2	5.1×10^{-2}	$1.0 - 3.3 \times 10^{-3}$
1,1,1-Trichloroethane (1,1,1-TCA)	D	—	—
Trichloroethylene (TCE)	B2	1.1×10^{-2}	1.3×10^{-2}
Vinyl chloride	A	2.3	0.295

Source: U.S. EPA http://www.epa.gov/iris.

EXAMPLE 4.2 Risk Assessment for Chloroform in Drinking Water

When drinking water is disinfected with chlorine an undesired byproduct, chloroform ($CHCl_3$), is formed. Suppose a 70-kg person drinks 2 L of water every day for 70 years with a chloroform concentration of 0.10 mg/L (the drinking water standard).

a. Find the upper-bound cancer risk for this individual.
b. If a city with 500,000 people in it also drinks the same amount of this water, how many extra cancers per year would be expected? Assume the standard 70-year lifetime.
c. Compare the extra cancers per year caused by chloroform in the drinking water with the expected number of cancer deaths from all causes. The cancer death rate in the United States is 193 per 100,000 per year.

Solution

a. From Table 4.9 we see that chloroform is a Class B2 probable human carcinogen with a potency factor of $6.1 \times 10^{-3}\ (\text{mg/kg-day})^{-1}$. Using (4.13), the chronic daily intake is

$$\text{CDI (mg/kg-day)} = \frac{\text{Average daily dose (mg/day)}}{\text{Body weight (kg)}}$$

$$= \frac{0.10\ \text{mg/L} \times 2\ \text{L/day}}{70\ \text{kg}} = 0.00286\ \text{mg/kg-day}$$

From (4.12), the incremental lifetime cancer risk is

$$\text{Risk} = \text{CDI} \times \text{Potency factor}$$

$$= 0.00286\ (\text{mg/kg-day}) \times 6.1 \times 10^{-3}\ (\text{mg/kg-day})^{-1} = 17.4 \times 10^{-6}$$

So over a 70-year period the upper-bound estimate of the probability that a person will get cancer from this drinking water is about 17 in one million.

b. If there are 17.4 cancers per million people over a 70-year period, then in any given year in a population of one-half million, the number of cancers caused by chloroform would be

$$500{,}000\ \text{people} \times \frac{17.4\ \text{cancer}}{10^{6}\ \text{people}} \times \frac{1}{70\ \text{yr}} = 0.12\ \text{cancers/yr}$$

c. The total number of cancer deaths that would be expected in a city of 500,000 would be

$$500{,}000\ \text{people} \times \frac{193\ \text{cancer/yr}}{100{,}000\ \text{people}} = 965\ \text{cancer deaths/yr}$$

It would seem that an additional 0.12 new cancers per year would not be detectable. ■

Once again, it is necessary to emphasize that the science behind a risk assessment calculation of the sort demonstrated in Example 4.2 is primitive, and there are enormous uncertainties associated with any particular answer so computed. There is still great value, however, to this sort of procedure since it does organize a mass of data into a format that can be communicated to a much wider audience, and it can greatly help that audience find legitimate perspectives based on that data. For example, it matters little whether the annual extra cancers associated with chloroform in the preceding

example are found to be 0.12 or even ten times as much, 1.2; the conclusion that the extra cancers would be undetectable would not change.

Another use for these risk calculations is to estimate the concentration of a contaminant in drinking water that would result in a politically acceptable risk level. Often that risk goal is 10^{-6} and the concentration that will produce that risk is called the *drinking water equivalent level* (DWEL). To find the DWEL, it is usually assumed that a 70-kg adult consumes 2 L of water per day. As Example 4.3 shows, we can find the DWEL from the potency factor using (4.12).

EXAMPLE 4.3 Drinking water concentration of chloroform for a 10^{-6} risk

Find the concentration of chloroform in drinking water that would result in a 10^{-6} risk for a 70-kg person who drinks 2 L/day throughout his or her entire lifetime.

Solution Rearranging (4.12) and using the potency factor from Table 4.9 gives

$$\text{CDI} = \frac{\text{Risk}}{\text{Potency factor}} = \frac{10^{-6}}{6.1 \times 10^{-3}\ (\text{kg-day/mg})} = 1.64 \times 10^{-4}\ (\text{mg/kg-day})$$

Since CDI is just the average daily intake divided by body mass, we can write

$$\text{CDI} = \frac{C(\text{mg/L}) \times 2\ \text{L/day}}{70\ \text{kg}} = 1.64 \times 10^{-4}\ (\text{mg/kg-day})$$

where C (mg/L) is the allowable concentration of chloroform. Solving for C gives

$$C = 70 \times 1.64 \times 10^{-4}/2 = 0.0057 \approx 6 \times 10^{-3}\ \text{mg/L} = 6\mu\text{g/L}$$

So a DWEL of 6 μg/L for chloroform would result in an upper-bound risk of 10^{-6}. ■

In Examples 4.2 and 4.3 it was assumed that everyone drinks 2 L of contaminated water every day for 70 years. When a risk assessment is made for exposures that do not last the entire lifetime, we need to develop the chronic daily intake a little more carefully.

If the contaminant is in drinking water, the CDI can be expressed as

$$\text{CDI} = \frac{\text{Concentration (mg/L)} \times \text{Intake rate (L/day)} \times \text{Exposure (days/life)}}{\text{Body weight (kg)} \times 70\ \text{(yr/life)} \times 365\ \text{(days/yr)}} \qquad (4.14)$$

where *Concentration* refers to the contaminant concentration, *Intake rate* is the amount of water ingested each day, and *Exposure* is the number of days in a lifetime that the person drinks contaminated water.

If the exposure route is inhalation of a contaminant, the chronic daily intake can be expressed as

$$\text{CDI} = \frac{\text{Concentration (mg/m}^3\text{)} \times \text{Intake rate (m}^3\text{/day)} \times \text{Exposure (days/life)}}{\text{Body weight (kg)} \times 70\ \text{(yr/life)} \times 365\ \text{(days/yr)}} \qquad (4.15)$$

where *Concentration* is the contaminant concentration in air, and the *Intake rate* is the amount of air inhaled during each day that the person is exposed to the contamination. Similar expressions can be used for consumption of contaminated food or soil and for dermal contact with contaminated soil. For some of these circumstances, the CDI needs to include an absorption factor if it is thought that the absorption rate by a human is different from the absorption rate of the test animals that were used to establish the dose-response curve.

EXAMPLE 4.4 An Occupational Exposure

Estimate the incremental cancer risk for a 60-kg worker exposed to a particular carcinogen under the following circumstances. Exposure time is 5 days per week, 50 weeks per year, over a 25-year period of time. The worker is assumed to breathe 20 m^3 of air per day. The carcinogen has a potency factor of 0.02 (mg/kg-day)$^{-1}$ and its average concentration is 0.05 mg/m^3.

Solution Since this is an inhalation exposure, we will use (4.15).

$$\text{CDI} = \frac{0.05\ \text{mg/m}^3 \times 20\ \text{m}^3\text{/day} \times 5\ \text{days/wk} \times 50\ \text{wk/yr} \times 25\ \text{yr}}{60\ \text{kg} \times 70\ \text{yr/life} \times 365\ \text{days/yr}}$$

$$= 0.0041\ \text{mg/kg-day}$$

Using (4.12), the upper-bound, incremental cancer risk is CDI × potency:

$$\text{Incremental risk} = 0.0041\ \text{mg/kg-day} \times 0.02\ (\text{mg/kg-day})^{-1} = 81 \times 10^{-6}$$

which is considerably higher than the usual goal of 10^{-6} risk. ■

The EPA has developed a set of recommended default values for daily intakes, exposures, and body weights to be used in risk calculations when more site-specific information is not available. Table 4.10 shows some of these default factors, and the next example illustrates their use.

EXAMPLE 4.5 A Proposed Source of Benzene in Your Neighborhood

Suppose an industrial facility that emits benzene into the atmosphere is being proposed for a site near a residential neighborhood. Air quality models predict that 60 percent of the time, prevailing winds will blow the benzene away from the neighborhood, but 40 percent of the time the benzene concentration will be 0.01 mg/m^3. Use standard exposure factors from Table 4.10 to assess the incremental risk to adults in the neighborhood if the facility is allowed to be built. If the acceptable risk is 10^{-6}, should this plant be allowed to be built?

Solution Using factors from Table 4.10, the chronic daily intake will be

$$CDI = \frac{0.01\ \text{mg/m}^3 \times 20\ \text{m}^3\text{/day} \times 350\ \text{day/yr} \times 30\ \text{yr}}{70\ \text{kg} \times 365\ \text{day/yr} \times 70\ \text{yr}} \times 0.40$$

$$= 0.00047\ \text{mg/kg-day}$$

The potency factor from Table 4.9 for benzene is 2.9×10^{-2} (mg/kg-day)$^{-1}$, so the incremental risk would be

$$\text{Incremental risk} = 0.00047\ \text{mg/kg-day} \times 2.9 \times 10^{-2}\ (\text{mg/kg-day})^{-1} = 1.3 \times 10^{-5}$$

The risk is higher than the acceptable level, so the facility should not be built as it is being proposed. ■

TABLE 4.10 Example EPA Exposure Factors Recommended for Risk Assessments

Land use	Exposure pathway	Daily intake	Exposure frequency, days/year	Exposure duration, years	Body weight, kg
Residential	Ingestion of potable water	2 L (adult) 1 L (child)	350	30	70 (adult) 15 (child)
	Ingestion of soil and dust	200 mg (child) 100 mg (adult)	350	6 24	15 (child) 70 (adult)
	Inhalation of contaminants	20 m^3 (adult) 12 m^3 (child)	350	30	70
Industrial and commercial	Ingestion of potable water	1 L	250	25	70
	Ingestion of soil and dust	50 mg	250	25	70
	Inhalation of contaminants	20 m^3 (workday)	250	25	70
Agricultural	Consumption of homegrown produce	42 g (fruit) 80 g (veg.)	350	30	70
Recreational	Consumption of locally caught fish	54 g	350	30	70

Source: U.S. EPA (1991).

The Reference Dose for Noncarcinogenic Effects

The key assumption for noncarcinogens is that there is an exposure threshold; that is, any exposure less than the threshold would be expected to show no increase in adverse effects above natural background rates. One of the principal goals of toxicant testing is therefore to identify and quantify such thresholds. Unfortunately, for the usual case, inadequate data are available to establish such thresholds with any degree of certainty and, as a result, it has been necessary to introduce a number of special assumptions and definitions.

Suppose there exists a precise threshold for some particular toxicant for some particular animal species. To determine the threshold experimentally, we might imagine a testing program in which animals would be exposed to a range of doses. Doses below the threshold would elicit no response; doses above the threshold would produce responses. The lowest dose administered that results in a response is given a special name: the *lowest-observed-effect level* (LOEL). Conversely, the highest dose administered that does not create a response is called the *no-observed-effect level* (NOEL). NOELs and LOELs are often further refined by noting a distinction between effects that are *adverse* to health and effects that are not. Thus, there are also *no-observed-adverse-effect levels* (NOAELs) and *lowest-observed-adverse-effect levels* (LOAELs).

Figure 4.11 illustrates these levels and introduces another exposure called the *reference dose*, or RfD. The RfD used to be called the *acceptable daily intake* (ADI), and as that name implies, it is intended to give an indication of a level of human exposure that is likely to be without appreciable risk. The units of RfD are mg/kg-day averaged over a lifetime, just as they were for the chronic daily intake CDI. The RfD is obtained by dividing the NOAEL by an appropriate *uncertainty factor* (sometimes called a safety factor). A 10-fold uncertainty factor is used to account for differences in sensitivity between the most sensitive individuals in an exposed human population, such as pregnant women, babies, and the elderly, and "normal, healthy" people. Another factor of 10 is introduced when the NOAEL is based on animal data that is to be extrapolated to humans. And finally, another factor of 10 is sometimes applied when there are no good human data and the animal data available are limited. Thus, depending on the strength of the available data, human RfD levels are established at doses that are anywhere from one-tenth to one-thousandth of the NOAEL, which is itself somewhat below the actual threshold. Table 4.11 gives a short list of some commonly encountered toxicants and their RfDs.

The Hazard Index for Noncarcinogenic Effects

Since the reference dose RfD is established at what is intended to be a safe level, well below the level at which any adverse health effects have been observed, it makes sense to compare the actual exposure to the RfD to see whether the actual dose is supposedly safe. The hazard quotient is based on that concept:

$$\text{Hazard quotient} = \frac{\text{Average daily dose during exposure period (mg/kg-day)}}{\text{RfD}} \tag{4.16}$$

Notice that the daily dose is averaged only over the period of exposure, which is different from the average daily dose used in risk calculations for carcinogens. For noncarcinogens, the toxicity is important only during the time of exposure. Recall that for a cancer risk calculation (e.g., Eq. 4.13) the dose is averaged over an assumed 70-year lifetime.

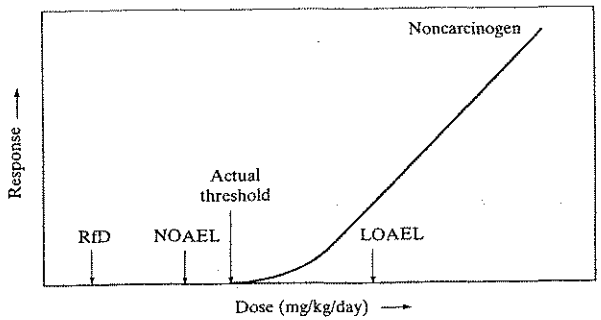

FIGURE 4.11 The reference dose RfD is the no-observed-adverse-effects-level (NOAEL) divided by an uncertainty factor typically between 10 and 1000.

TABLE 4.11 Oral RfDs for chronic noncarcinogenic effects of selected chemicals.

Chemical	RfD (mg/kg-day)
Acetone	0.100
Arsenic	0.0003
Cadmium	0.0005
Chloroform	0.010
1,1-dichloroethylene	0.009
cis-1,2-Dichloroethylene	0.010
Fluoride	0.120
Mercury (inorganic)	0.0003
Methylene chloride	0.060
Phenol	0.600
Tetrachloroethylene	0.010
Toluene	0.200
1,1,1-Trichloroethane	0.035
Xylene	2.000

Source: U.S. EPA. http://www.epa.gov/iris

The hazard quotient has been defined so that if it is less than 1.0, there should be no significant risk of systemic toxicity. Ratios above 1.0 could represent a potential risk, but there is no way to establish that risk with any certainty.

When exposure involves more than one chemical, the sum of the individual hazard quotients for each chemical is used as a measure of the potential for harm. This sum is called the *hazard index:*

$$\text{Hazard index} = \text{Sum of the hazard quotients} \tag{4.17}$$

EXAMPLE 4.6 Hazard Index

Suppose drinking water contains 1.0 mg/L of toluene and 0.01 mg/L of tetrachloroethylene (C_2Cl_4). A 70-kg adult drinks 2 L per day of this water for 10 years.

a. Would the hazard index suggest that this was a safe level of exposure?

b. Tetrachloroethylene is a B2 carcinogen. What would be the carcinogenic risk faced by someone drinking this water? Would it be less than a goal of 10^{-6}?

Solution

a. First we need to find the average daily doses (ADDs) for each of the chemicals and then their individual hazard quotients.

For toluene, the RfD is given in Table 4.11 as 0.200 mg/kg-day, so

$$\text{ADD (toluene)} = \frac{1.0 \text{ mg/L} \times 2 \text{ L/day}}{70 \text{ kg}} = 0.029 \text{ mg/kg-day}$$

$$\text{Hazard quotient (toluene)} = \frac{0.029 \text{ mg/kg-day}}{0.200 \text{ mg/kg-day}} = 0.14$$

The RfD for tetrachloroethylene is 0.01 mg/kg-day, so

$$\text{ADD } (C_2Cl_4) = \frac{0.01 \text{ mg/L} \times 2 \text{ L/day}}{70 \text{ kg}} = 0.00029 \text{ mg/kg-day}$$

$$\text{Hazard quotient } (C_2Cl_4) = \frac{0.00029 \text{ mg/kg-day}}{0.01 \text{ mg/kg-day}} = 0.029$$

So

$$\text{Hazard index} = 0.14 + 0.029 = 0.17 < 1.0$$

The hazard index suggests that this water is safe. By the way, notice that we did not need to know that the person drank this water for 10 years.

b. The incremental carcinogenic risk associated with the C_2Cl_4 is

$$\text{Risk} = \text{CDI} \times \text{Potency factor}$$

$$\text{CDI} = \frac{0.01 \text{ mg/L} \times 2 \text{ L/day} \times 365 \text{ days/yr} \times 10 \text{ yrs}}{70 \text{ kg} \times 365 \text{ days/yr} \times 70 \text{ yrs}} = 4.0 \times 10^{-5} \text{ mg/kg-day}$$

From Table 4.9 the oral potency is 5.1×10^{-2} (mg/kg-day)$^{-1}$, so the risk is

$$\text{Risk} = \text{CDI} \times \text{Potency factor}$$
$$= 4.0 \times 10^{-5} \text{ mg/kg-day} \times 5.1 \times 10^{-2} \text{ (mg/kg-day)}^{-1} = 2 \times 10^{-6}$$

So, from a cancer risk standpoint, this water does not meet the 10^{-6} risk goal. Notice how the tetrachloroethylene was way below the RfD but was above the desired risk goal. This is not uncommon when the hazard index is computed for carcinogens. ■

4.7 HUMAN EXPOSURE ASSESSMENT

One of the most elementary concepts of risk assessment is one that is all too often overlooked in public discussions: that risk has two components—the toxicity of the substance involved, and the amount of exposure to that substance. Unless individuals are exposed to the toxicants, there is no human risk.

A human exposure assessment is itself a two-part process. First, pathways that allow toxic agents to be transported from the source to the point of contact with people must be evaluated. Second, an estimate must be made of the amount of contact that is likely to occur between people and those contaminants. Figure 4.12 suggests some of the transport mechanisms that are common at a toxic waste site. Substances that are exposed to the atmosphere may volatilize and be transported with the prevailing winds (in which case, plume models such as the ones introduced in Chapter 7 are often used). Substances in contact with soil may leach into groundwater and eventually be transported to local drinking water wells (groundwater flows will be analyzed in Chapter 5). As pollutants are transported from one place to another, they may undergo various transformations that can change their toxicity and/or concentration. Many of these fate and transport pathways for pollutants will be covered later in this book. A useful summary of exposure pathway models that the EPA uses is given in the Superfund Exposure Assessment Manual (U.S. EPA, 1988).

Once the exposure pathways have been analyzed, an estimate of the concentrations of toxicants in the air, water, soil, and food at a particular exposure point can be

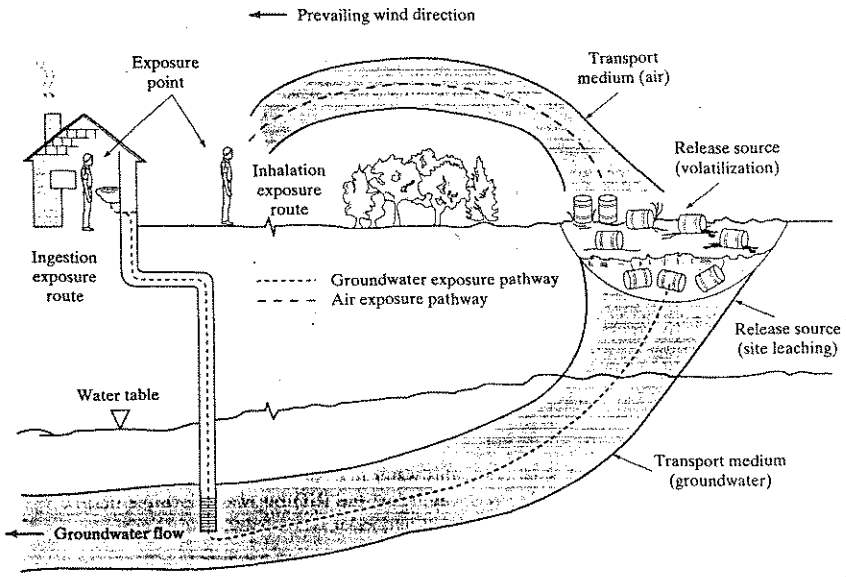

FIGURE 4.12 Illustration of exposure pathways. (Source: U.S. EPA, 1986b)

made. With the concentrations of various toxic agents established, the second half of an exposure assessment begins. Human contact with those contaminants must be estimated. Necessary information includes numbers of people exposed, duration of exposure, and amounts of contaminated air, water, food, and soil that find their way into each exposed person's body. Often, the human intake estimates are based on a lifetime of exposure, assuming standard, recommended daily values of amounts of air breathed, water consumed, and body weight, such as are given in Table 4.10. In some circumstances, the exposure may be intermittent and adjustments might need to be made for various body weights, rates of absorption, and exposure periods, as was illustrated in Example 4.4.

Bioconcentration

One potentially important exposure route is human consumption of contaminated fish. It is relatively straightforward to estimate concentrations of contaminants in water, and it also is reasonable to make estimates of consumption of fish that individuals may consume (for example, the standard intake values given in Table 4.10). What is more difficult is the task of estimating the concentration of a contaminant in fish, given only the chemical concentration in water. The *bioconcentration factor* (BCF) provides the key link. It is a measure of the tendency for a substance to accumulate in fish tissue. The equilibrium concentration of a chemical in fish can be estimated by multiplying the chemical concentration in water by the bioconcentration factor:

$$\text{Concentration in fish} = (\text{concentration in water}) \times (\text{bioconcentration factor}) \quad (4.18)$$

The units of BCF (L/kg) are picked to allow the concentration of substance in water to be the usual mg/L and the concentration in fish to be milligrams of substance per kilogram of fish. Some example values of BCF are given in Table 4.12. Note the high bioconcentration factors for chlorinated hydrocarbon pesticides, such as chlordane, DDT, and heptachlor, and the especially high concentration factor for polychlorinated biphenyls (PCBs). These high bioconcentration factors played an important role in the decision to reduce or eliminate the use of these chemicals in the United States.

The following example illustrates the use of bioconcentration factors in a carcinogenic risk assessment.

TABLE 4.12 Bioconcentration Factors (BCFs) for a Selected List of Chemicals.

Chemical	Bioconcentration Factor (L/kg)
Aldrin	28
Arsenic and compounds	44
Benzene	5.2
Cadmium and compounds	81
Carbon tetrachloride	19
Chlordane	14,000
Chloroform	3.75
Chromium III, VI, and compounds	16
Copper	200
DDE	51,000
DDT	54,000
1,1-Dichloroethylene	5.6
Dieldrin	4760
Formaldehyde	0
Heptachlor	15,700
Hexachloroethane	87
Nickel and compounds	47
Polychlorinated biphenyls (PCBs)	100,000
2,3,7,8-TCDD (Dioxin)	5000
Tetrachloroethylene	31
1,1,1-Trichloroethane	5.6
Trichloroethylene (TCE)	10.6
Vinyl chloride	1.17

Source: U.S. EPA (1986b).

EXAMPLE 4.7 Bioconcentration of TCE

Using the standard exposure factors in Table 4.10 for a person eating locally caught fish, estimate the lifetime cancer risk from fish taken from waters containing a concentration of trichloroethylene (TCE) equal to 100 ppb (0.1 mg/L).

Solution In Table 4.12 the bioconcentration factor for TCE is given as 10.6 L/kg. From (4.18) the expected concentration of TCE in fish is therefore

$$\text{TCE concentration} = 0.1 \text{ mg/L} \times 10.6 \text{ L/kg} = 1.06 \text{ mg TCE/kg fish}$$

From Table 4.10, standard exposure factors include a 70-kg person consuming 54g of fish, 350 days per year for 30 years. The chronic daily intake CDI is thus

$$CDI = \frac{0.054\ \text{kg/day} \times 1.06\ \text{mg TCE/kg} \times 350\ \text{days/yr} \times 30\text{yrs}}{70\ \text{kg} \times 365\ \text{days/yr} \times 70\ \text{yrs}}$$
$$= 3.36 \times 10^{-4}\ \text{mg/kg-day}$$

From Table 4.9 the cancer potency factor for an oral dose of TCE is $1.1 \times 10^{-2}(\text{mg/kg-day})^{-1}$. Using (4.12), the upper-bound, incremental lifetime risk of cancer is

$$\text{Risk} = \text{CDI} \times \text{potency factor}$$
$$= 3.36 \times 10^{-4}\ \text{mg/kg-day} \times 1.1 \times 10^{-2}\ (\text{mg/kg-day})^{-1} = 3.6 \times 10^{-6}$$

or about 4 in 1 million. ■

Contaminant Degradation

Many toxic chemicals of concern are nonconservative; that is, they degrade with time. Degradation may be the result of a number of processes that remove pollutants from the medium in which they reside. There may be phase transfer as a chemical volatilizes; chemical transformation if it reacts with other substances; or biological transformation if it is consumed by microorganisms. The persistence of a chemical as it moves through various environmental media may be affected by some combination of these mechanisms. A convenient way to deal with such complexity is simply to combine the degradation processes into a single, overall *half-life*. The half-life of a given substance will depend on whether it appears in soil, air, surface water, or groundwater. Some representative half-lives are given in Table 4.13.

TABLE 4.13 Range of Half-Lives (days) of Various Contaminants in Air and Surface Water

	Air		Surface Water	
Chemical	Low	High	Low	High
Benzene	6	—	1	6
Benzo(a)pyrene	1	6	0.4	—
Carbon Tetrachloride	8030	—	0.3	300
Chlordane	40	—	420	500
Chloroform	80	—	0.3	30
DDT	—	—	56	110
1,1-Dichloroethane	45	—	1	5
Formaldehyde	0.8	—	0.9	3.5
Heptachlor	40	—	0.96	—
Hexachloroethane	7900	—	1.1	9.5
Polychlorinated biphenyls (PCBs)	58	—	2	12.9
2,3,7,8-TCDD (Dioxin)	—	—	365	730
1,1,1-Trichloroethane	803	1752	0.14	7
Trichloroethylene	3.7	—	1	90
Vinyl chloride	1.2	—	1	5

Source: U.S. EPA (1986b).

The relationship between reaction rate coefficient K and half-life ($T_{1/2}$) was derived in Chapter 3. Recall that if the concentration of a substance is modeled with a simple exponential decay relationship,

$$C(t) = C(0)e^{-Kt} \tag{4.19}$$

then the time required for the concentration to be decreased by 50 percent is the half-life, given by

$$T_{1/2} = \frac{\ln 2}{K} = \frac{0.693}{K} \tag{4.20}$$

An example of how to use half lives is given in the following example.

EXAMPLE 4.8 A Leaking Underground Storage Tank Exposure Assessment

Suppose an underground storage tank has been leaking for many years, contaminating the groundwater and causing a contaminant concentration directly beneath the site of 0.30 mg/L. The contamination is flowing at the rate of 0.5 ft per day toward a public drinking water well 1 mile away. The half-life of the contaminant is 10 years.

a. Estimate the steady-state pollutant concentration expected at the well.

b. If the potency factor for the contaminant is 0.02 $(\text{mg/kg-day})^{-1}$, estimate the cancer risk if a 70-kg person drank 2 L of this water per day for 10 years.

Solution

a. The time required to travel to the well 1 mile away would be

$$\text{Time to well} = \frac{5280\ \text{ft}}{0.5\ \text{ft/day}} = 10{,}560\ \text{days}$$

The pollutant is assumed to degrade exponentially, so the reaction rate coefficient K can be found using (4.20):

$$K = \frac{0.693}{T_{1/2}} = \frac{0.693}{10\ \text{yr} \times 365\ \text{days/yr}} = 1.9 \times 10^{-4}/\text{day}$$

In the 10,560 days required to travel to the drinking water well, (4.19) suggests that the initial 0.30 mg/L would be reduced to

$$C(t) = C(0)e^{-Kt} = 0.30e^{-(1.9 \times 10^{-4}/d \times 10{,}560\ d)} = 0.040\ \text{mg/L}$$

b. The chronic daily intake for someone drinking this water for 10 years out of a 70-year lifetime would be

$$\text{CDI} = \frac{0.040\ \text{mg/L} \times 2\ \text{L/day} \times 10\ \text{yr}}{70\ \text{kg} \times 70\ \text{yr}} = 1.6 \times 10^{-4}\ \text{mg/kg-day}$$

so the lifetime cancer risk would be

$$\text{Risk} = \text{CDI} \times \text{potency factor}$$
$$= 1.6 \times 10^{-4}\ \text{mg/kg-day} \times 0.020\ (\text{mg/kg-day})^{-1} = 3.2 \times 10^{-6}$$

This is probably an upper-bound estimate of the individual risk and is subject to all of the uncertainties that currently characterize all risk assessments. ■

4.8 RISK CHARACTERIZATION

The final step in a risk assessment is to bring the various studies together into an overall risk characterization. In its most primitive sense, this step could be interpreted to mean simply multiplying the exposure (dose) by the potency to get individual risk, and then multiplying that by the number of people exposed to get an estimate of overall risk to some specific population.

While there are obvious advantages to presenting a simple, single number for extra cancers, or some other risk measure, a proper characterization of risk should be much more comprehensive. The final expressions of risk derived in this step will be used by regulatory decision makers in the process of weighing health risks against other societal costs and benefits, and the public will use them to help them decide on the adequacy of proposed measures to manage the risks. Both groups need to appreciate the extraordinary leaps of faith that, by necessity, have had to be used to determine these simple quantitative estimates. It must always be emphasized that these estimates are preliminary, subject to change, and extremely uncertain.

The National Academy of Sciences (1983) suggests a number of questions that should be addressed in a final characterization of risk, including the following:

- What are the statistical uncertainties in estimating the extent of health effects? How are these uncertainties to be computed and presented?
- What are the biological uncertainties? What are their origins? How will they be estimated? What effect do they have on quantitative estimates? How will the uncertainties be described to agency decision makers?
- Which dose-response assessments and exposure assessments should be used?
- Which population groups should be the primary targets for protection, and which provide the most meaningful expression of the health risk?

Rodricks (page 181, 1992) offers the following example of the sort of qualifying statement that ought to accompany all risk assessments (in this case for a hypothetical contaminant difluoromuckone, DFM):

> Difluoromuckone (DFM) has been found to increase the risk of cancer in several studies involving experimental animals. Investigations involving groups of individuals exposed in the past to relatively high levels of DFM have not revealed that the chemical increases cancer risk in humans. Because these human studies could not detect a small increase in risk, and because there is a scientific basis for assuming results from animal experiments are relevant to humans, exposure to low levels of DFM may create an increase in risk of cancer for people. The magnitude of this risk is unknown, but probably does not exceed one in 50,000. This figure is the lifetime chance of developing cancer from a daily exposure to the highest levels of DFM detected in the environment. Average levels, which are more likely to be experienced over the course of a lifetime, suggest a lifetime risk more like one in 200,000. These risk figures were derived using scientific assumptions that are not recognized as plausible by all scientists, but which are consistently used by regulatory scientists when attempting to portray the risks of environmental chemicals. It is quite plausible that actual risks are lower than the ones cited above; higher risks are not likely but cannot be ruled out. Regulators typically seek to reduce risks that exceed a range of one in 100,000 to one in 1,000,000. Note that the lifetime cancer risk we face from all sources of these diseases is about 1 in 5 (1 in 10 for non-smokers), so that, even if correct, the DFM risk is a minor contributor to the overall cancer problem. Prudence may dictate the need for some small degree of risk reduction for DFM in the environment.

4.9 COMPARATIVE RISK ANALYSIS

In 1987, the EPA released a report entitled *Unfinished Business: A Comparative Assessment of Environmental Problems* (U.S. EPA, 1987), in which the concepts of risk assessment were applied to a variety of pressing environmental problems. The goal of the study was to attempt to use risk as a policy tool for ranking major environmental problems in order to help the agency establish broad, long-term priorities.

At the outset it was realized that direct comparisons of different environmental problems would be next to impossible. Not only are the data usually insufficient to quantify risks, but the kinds of risk associated with some problems, such as global warming, are virtually incomparable with risks of others, such as hazardous waste. In most cases, considerable professional judgment rather than hard data was required to finalize the EPA's rankings. In spite of difficulties such as these, the report is noteworthy both in terms of its methodology and its conclusions.

The study was organized around a list of 31 environmental problems, including topics as diverse as conventional (criteria) air pollutants, indoor radon, stratospheric ozone depletion, global warming, active hazardous waste sites regulated by the Resource Conservation and Recovery Act (RCRA), and inactive (Superfund) hazardous waste sites, damage to wetlands, mining wastes, and pesticide residues on foods. Each of these 31 problems was analyzed in terms of four different types of risk: cancer risks, noncancer health risks, ecological effects, and welfare effects (visibility impairment, materials damage, etc.). In each assessment, it was assumed that existing environmental control programs continue so that the results represent risks as they exist now, rather than what they would have been had abatement programs not already been in place.

The ranking of cancer risks was perhaps the most straightforward part of the study since the EPA has already established risk assessment procedures and there are considerable data already available from which to work. Rankings were based primarily on overall cancer risk to the entire U.S. population, although high risks to specific groups of individuals, such as farm workers, were noted. A number of caveats were emphasized in the final rankings on such issues as lack of complete data, uneven quality of data, and the usual uncertainties in any risk assessment that arise from such factors as interspecies comparisons, adequacy of the low-dose extrapolation model, and estimations of exposures. Ordinal rankings were given, but it was emphasized that these should not be interpreted as being precise, especially when similarly ranked problems are being compared.

Given all of the uncertainties, in the cancer working group's final judgment two problems were tied at the top of the list: (1) worker exposure to chemicals, which does not involve a large number of individuals but does result in high individual risks to those exposed; and (2) indoor radon exposure, which is causing significant risk to a

large number of people. Inactive (Superfund) hazardous waste sites ranked eighth and active (RCRA) hazardous waste sites were thirteenth. Interestingly, it was noted that with the exception of pesticide residues on food, the major route of exposure for carcinogens is inhalation. Their final ranking of carcinogenic risks is reproduced in Table 4.14.

The other working groups had considerably greater difficulty ranking the 31 environmental problem areas since there are no accepted guidelines for quantitatively assessing relative risks. As noted in *Unfinished Business*, a perusal of the rankings of the 31 problem areas for each of the four types of risk (cancer, noncancer health effects, ecological, and welfare effects) produced the following general results:

TABLE 4.14 Consensus Ranking of Environmental Problem Areas on the Basis of Population Cancer Risk

Rank	Problem Area	Selected Comments
1 (tied)	Worker exposure to chemicals	About 250 cancer cases per year estimated based on exposure to 4 chemicals; but workers face potential exposures to over 20,000 substances. Very high individual risk possible.
1 (tied)	Indoor radon	Estimated 5000 to 20,000 lung cancers annually from exposure in homes.
3	Pesticide residues on foods	Estimated 6000 cancers annually, based on exposure to 200 potential carcinogens.
4 (tied)	Indoor air pollutants (nonradon)	Estimated 3500 to 6500 cancers annually, mostly due to tobacco smoke.
4 (tied)	Consumer exposure to chemicals	Risk from 4 chemicals investigated is about 100 to 135 cancers annually; an estimated 10,000 chemicals in consumer products. Cleaning fluids, pesticides, particleboard, and asbestos-containing products especially noted.
6	Hazardous/toxic air pollutants	Estimated 2000 cancers annually based on an assessment of 20 substances.
7	Depletion of stratospheric ozone	Ozone depletion projected to result in 10,000 additional annual deaths in the year 2100. Not ranked higher because of the uncertainties in future risk.
8	Hazardous waste sites, inactive	Cancer incidence of 1000 annually from 6 chemicals assessed. Considerable uncertainty since risk based on extrapolation from 35 sites to about 25,000 sites.
9	Drinking water	Estimated 400 to 1000 annual cancers, mostly from radon and trihalomethanes.
10	Application of pesticides	Approximately 100 cancers annually; small population exposed but high individual risks.
11	Radiation other than radon	Estimated 360 cancers per year. Mostly from building materials. Medical exposure and natural background levels not included.
12	Other pesticide risks	Consumer and professional exterminator uses estimated cancers of 150 annually. Poor data.
13	Hazardous waste sites, active	Probably fewer than 100 cancers annually; estimates sensitive to assumptions regarding proximity of future wells to waste sites.

TABLE 4.14 Continued

Rank	Problem Area	Selected Comments
14	Nonhazardous waste sites, industrial	No real analysis done, ranking based on consensus of professional opinion.
15	New toxic chemicals	Difficult to assess; done by consensus.
16	Nonhazardous waste sites, municipal	Estimated 40 cancers annually, not including municipal surface impoundments.
17	Contaminated sludge	Preliminary results estimate 40 cancers annually, mostly from incineration and landfilling.
18	Mining waste	Estimated 10 to 20 cancers annually, largely due to arsenic. Remote locations and small population exposure reduce overall risk though individual risk may be high.
19	Releases from storage tanks	Preliminary analysis, based on benzene, indicated low cancer incidence (< 1).
20	Nonpoint-source discharges to surface water	No quantitative analysis available; judgment.
21	Other groundwater contamination	Lack of information; individual risks considered less than 10^{-6}, with rough estimate of total population risk at < 1.
22	Criteria air pollutants	Excluding carcinogenic particles and volatile organic chemicals (VOCs) (included under Hazardous/Toxic Air Pollutants); ranked low because remaining criteria pollutants have not been shown to be carcinogens.
23	Direct point-source discharges to surface water	No quantitative assessment available. Only ingestion of contaminated seafood was considered.
24	Indirect,point-source discharges to surface water	Same as above.
25	Accidental releases—toxics	Short-duration exposure yields low cancer risk; noncancer health effects of much greater concern.
26	Accidental releases—oil spills	See above. Greater concern for welfare and ecological effects.

Not ranked: Biotechnology; global warming; other air pollutant; discharges to estuaries, costal waters and oceans; discharges to wetlands/

Source: Based on data from U.S. EPA (1987).

- No problems rank relatively high in all four types of risk, or relatively low in all four.
- Problems that rank relatively high in three of the four risk types, or at least medium in all four, include criteria air pollutants (see Chapter 7); stratospheric ozone depletion (Chapter 8); pesticide residues on food; and other pesticide risks (runoff and air deposition of pesticides).
- Problems that rank relatively high in cancer and noncancer health risks, but low in ecological and welfare risks, include hazardous air pollutants; indoor radon; indoor air pollution other than radon; pesticide application; exposure to consumer products; and worker exposures to chemicals.
- Problems that rank relatively high in ecological and welfare risks, but low in both health risks, include global warming; point and nonpoint sources of surface water

pollution; physical alteration of aquatic habitats (including estuaries and wetlands), and mining wastes.

- Areas related to groundwater consistently rank medium or low.

In spite of the great uncertainties involved in making their assessments, the divergence between the EPA effort in the 1980s and relative risks is noteworthy. As concluded in the study, areas of relatively high risk but low EPA effort include indoor radon; indoor air pollution; stratospheric ozone depletion; global warming; nonpoint sources; discharges to estuaries, coastal waters, and oceans; other pesticide risks; accidental releases of toxics; consumer products; and worker exposures. Areas of high EPA effort but relatively medium or low risks include RCRA sites, Superfund sites, underground storage tanks, and municipal nonhazardous waste sites.

The *Unfinished Business* report was the first major example of what has come to be known as *comparative risk analysis.* Comparative risk analysis differs from conventional risk assessment since its purpose is not to establish absolute values of risk, but rather to provide a process for ranking environmental problems by their seriousness. A subsequent 1990 report, *Reducing Risks,* by EPA's Science Advisory Board, recommended that the EPA reorder its priorities on the basis of reducing the most serious risks. The combination of these two reports has had considerable influence on the way that the EPA perceives its role in environmental protection. EPA's Office of Research and Development (U.S. EPA, 1996) has incorporated these recommendations in setting forth its strategic principles, which include the following:

- Focus research and development on the greatest risks to people and the environment, taking into account their potential severity, magnitude, and uncertainty.
- Focus research on reducing uncertainty in risk assessment and on cost-effective approaches for preventing and managing risks.
- Balance human health and ecological research.

Based on those strategic principles, the EPA has recently defined its six highest-priority research topics for the next few years (U.S. EPA, 1996):

- *Drinking water disinfection.* Some microorganisms, especially the protozoan *Cryptosporidium,* are able to survive conventional disinfection processes, and some carcinogens, such as chloroform, are created during chlorination of drinking water. Questions to be addressed include the comparative risk between waterborne microbial disease and the disinfection byproducts formed during drinking water disinfection.
- *Particulate matter.* Inhalation of particulate matter in the atmosphere poses a high potential human health risk. The relationship between morbidity/mortality and low ambient levels of particulate matter, and cost-effective methods to reduce particulate matter emissions, are principle areas of interest.
- *Endocrine disruptors.* Declines in the quality and quantity of human sperm production and increased incidence of certain cancers that may have an endocrine-related basis form the basis of concern for this high-priority research topic.
- *Improved ecosystem risk assessment.* Understanding the impacts of human activities on ecosystems has not developed as rapidly as human health impacts. Topics such as forest decline, toxic microorganisms in estuaries, reproductive failure of wildlife, and the reappearance of vectorborne epidemic diseases need to be addressed.
- *Improved health risk assessment.* Continued focus on reducing the uncertainty in source-exposure-dose relationships, including the impacts of mixtures of chemical insults, is needed.
- *Pollution prevention and new technologies.* Avoiding the creation of environmental problems is the most cost-effective risk-management strategy, but it is not clear how best to integrate pollution prevention into government and private-sector decision making.