chapter twenty-one

Risk assessment, risk evaluation, and risk management

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21.1 Introduction

Most human activities carry some degree of risk. Many risks are known to a relatively high degree of accuracy, because data have been collected on their historical occurrence. For example, the number of deaths caused by motor vehicle accidents in 1 year is divided by the total number of people at risk (e.g., the entire US population) for an actual individual risk of 1/4500 from dying of such an accident. Based on a 70-year lifetime, people in the US have a 1/65 probability of dying in a car accident over an entire lifetime.

The risks associated with many other activities, including exposure to food-borne microbes or various substances found in or associated with food, cannot be readily assessed or quantified. Considerable historical data exist on the risks of some types of chemical or microbial exposure (e.g., the annual risks of death from intentional overdoses or accidental exposures to drugs, pesticides, and industrial chemicals, or the annual risk of food-borne disease). Such data, however, are usually restricted to those situations in which a single high exposure resulted in an immediately observable form of disease or injury, thus leaving little doubt about the cause. Assessment of the risks of exposures to

substances or microbes that do not cause immediately observable forms of injury or disease (or only minor forms such as transient eye or skin irritation) is far more complex.

This type of risk assessment is of great concern to scientists and those involved in regulation and, just as importantly, to the general public. For industries associated with food and food production, as well as any type of chemical, food additive, or drug, the health risk assessment associated with the substance is critically important.

Some confusion exists regarding the terms used in microbial and chemical risk assessment since many are commonly used but have slightly different meanings. The term risk, and terms associated with it, such as safety, form an example of the difficulties that can arise when scientists and technical experts use common words in a context different from everyday language. For example, safety — the probability that harm will not occur under specified conditions — has been described as the converse of risk. This probabilistic statement clearly differs from the common definition associated with safe, which suggests "free from harm or risk." In addition, slightly different terms are used in the US, Europe, Japan, and the global scientific community for similar topics or procedures.

Understanding the hazards associated with food is also complex because food safety and food safety assessment rely on two different scientific disciplines: one concerned with assessing the microbiological safety and the other with assessing the chemical (or toxicological) safety of food. In the first case, the microbiological hazards and risks associated with preparation and storage of foods in all links of the food chain must be controlled and evaluated. In the second case, the toxicological risks from substances present in food must be assessed and evaluated. The terms used to describe these two areas are not rigidly defined. The microbiological hazards may include toxic substances of microbial origin. The term chemical risk assessment generally refers to assessment of synthetic substances to which humans may be exposed. The term toxicological risk assessment emphasizes the potential toxic effects of substances, and is also referred to as biological risk assessment, which emphasizes the biological effects of substances. In this chapter the term chemical risk assessment will be used.

21.2 Elements of hazard and risk

Risk is the probability of injury, disease, or death under specific circumstances. A hazard is a set of circumstances that may cause adverse effects, and the likelihood that a hazard will cause such effects is the risk associated with it. Risk may be expressed in quantitative terms, taking values from zero (certainty that harm will not occur) to one (certainty that it will). In many cases, risk can only be described qualitatively, as, for example, high, low, or minimal.

For example, a speeding car constitutes a hazard. The faster the car is driven, the more cars or people in the vicinity of the speeding car, the higher the risk that someone will be injured or killed. All hazards do not pose the same risks. The circumstances must be such that there is a likelihood of injury, harm, or death.

21.3 Microbial risks associated with food

Among the classes of hazards associated with food, microbial and viral contamination of the food supply are among the most important. Table 21.1 provides a list of microorganisms associated with food contamination and illness, and their principal food sources. For the most part, the sources of contamination are well-known microorganisms found in poultry, eggs, dairy products, and meat, and associated with improper handling. If these microbiological hazards are not controlled, this may result in a shorter shelf life of products, spoilage, and food-borne illnesses. Although the yearly number of reported illnesses

Table 21.1 Microorganisms and their principal food sources associated with food contamination and illness

Microorganism	Food source
Salmonella	Raw meat and poultry, raw milk, eggs
Clostridium perfringens	Meats, poultry, dried foods, herbs, spices, vegetables
Staphylococcus aureus	Cold foods (handled during preparation), dairy products, especially if prepared from raw milk
Bacillus cereus and other *Bacillus spp*	Cereals, dried foods, dairy products, meat and meat products, herbs, spices
Escherichia coli	Many raw foods
Vibrio parahaemolyticus	Raw and cooked fish, shellfish, and other seafoods
Yersinia enterocolitica	Raw meat and poultry, meat products, milk and milk products, vegetables
Campylobacter jejune	Raw poultry, meat, raw or inadequately heat treated milk, untreated water
Listeria monocytogenes	Meat, poultry, dairy products, vegetables. shellfish
Viruses	Raw shellfish, cold foods prepared by infected food handlers

Source: Roberts, 1990. With permission.

related to the consumption of contaminated food in the US is only a few thousand (because of their generally transient and innocuous character), estimates of the actual total number of cases vary between 20 and 40 million.

Traditional approaches to food safety, hygiene, protection, and sanitation have not made a significant impact in reducing reported food-borne diseases, even in developed countries. Inspection has been the major process in microbiological food safety programs. Inspection programs, however, have serious limitations, including the practice of observing only part of an operation and overlooking critical factors. Vague laws and the lack of giving priority to compliance also limit the effectiveness of food safety programs. Other approaches that have major limitations include inadequate or faulty microbiological testing and examination of workers or their tissue, urine, or blood specimens. A different approach — the Hazard Analysis and Critical Control Point (HACCP) system has been developed to attempt to make a significant impact on food-borne disease.

HACCP consists of a series of interrelated actions that should be taken to ensure the safety of all processed and prepared foods at critical points during production, storage, transport, processing, marketing, preparation, and service (see Table 21.2). The uses and applications of this system are discussed in *Microorganisms in Food* published in 1988 by the

Table 21.2 Hazard analysis and critical control point (HACCP) system

Determine hazards and assess their severity and risks
Identify critical control points
Institute control measures and establish criteria to ensure control
Monitor critical control points
Take action whenever monitoring results indicate criteria are not met
Verify that the system is functioning as planned

Source: Bryan, 1992. With permission.

International Commission on Microbiological Specifications for Food as well as in other international publications.

Although the public perceives that the toxicological risks from manufactured or synthetic chemicals (food additives, pesticides, etc.) are greater than microbiological risks, the scientific evidence does not support this perception.

In a nationwide survey in the US in 1990 entitled, "The Environment: Public Attitudes and Individual Behavior," a random sample of people were questioned about such environmental concerns as water pollution from industrial waste products, radiation from X-rays and microwave ovens, and pesticide residues in food eaten by humans. More than half of those surveyed indicated concern over pesticide residues in food. Of the food safety issues of concern to scientists, microbial contamination of the food supply has been identified as the most important food safety issue to affect public health in industrialized countries. This issue does not receive the public attention it deserves.

Estimation of the risk associated with microbiological contamination of foods suggests that the risk of morbidity, that is, the number of people who become ill, is in the order of 1 in 100 in a given year, while the risk of mortality, that is, the number of people who die directly or indirectly as a result of exposure to food-borne pathogens, is approximately 1 in 100,000 in a given year. Such risks should be compared with those associated with pesticide residues in food, which are in the order of 10^{-6} to 10^{-8}, and risks associated with naturally occurring toxic substances in foods, particularly carcinogens, which may be in the order of 10^{-3} or 10^{-4}.

21.4 Elements of chemical risk assessment

Risk assessment is the tool used to evaluate the safety of food and food additives. As noted by the Joint FAO/WHO (Food and Agricultural Organization of the World Health Organization) Expert Committee on Food Additives (JECFA) safety evaluation of food additives is a two-stage process. In the first stage relevant data are collected, including results of studies on experimental animals and, where possible, human observations, including epidemiology studies. In the second stage data are assessed to determine whether a substance is acceptable for its intended use as a food additive. This scientific process determines the possible adverse effects in humans resulting from exposure to a substance.

In 1983, the US National Academy of Science (NAS) issued a report entitled *Risk Assessment in the Federal Government: Managing the Process*. The report delineated research, risk assessment, and risk management, but emphasized the separation between the scientific exercise of risk assessment, and the policy exercise of risk management (Figure 21.1). The NAS report gave a formalized structure to the risk assessment process. It described four elements: *hazard identification* (see Section 21.4.1), *dose–response assessment* (see Section 21.4.2), *exposure assessment* (see Section 21.4.3), and *risk characterization* (see Section 21.4.4), with recommendations and examples given for the types of scientific information needed for each element.

Risk assessment was defined as the process of assessing the possible adverse health effects in humans resulting from exposure to substances or other potential hazards. This definition allows ordering of the data, identifying data gaps and uncertainties, assigning priorities, and determining research needs. Based on the information in the risk assessment, a regulatory agency can then develop regulatory options, evaluate the public health, economic, social, and political consequences of the regulatory options, and implement agency decisions and actions. These decisions and actions are the core of the risk management process. The four elements associated with risk assessment (see Figure 21.1) are briefly described in the following sections. The types of information used in health risk assessment are summarized in Table 21.3.

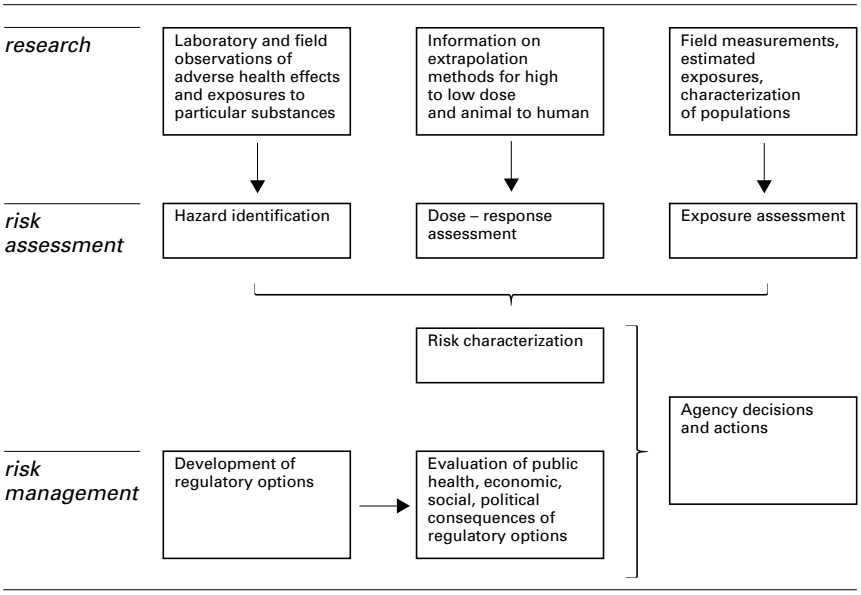

Figure 21.1 Elements of risk assessment and risk management. Reprinted with permission from Risk Assessment in the Federal Government. Copyright 1983, National Academy of Sciences. Courtesy of the National Academy Press, Washington, D.C.

21.4.1 Hazard identification

In the first step of hazard identification, data are gathered and evaluated on the types of health injury or disease that might be caused by a substance and on the conditions of exposure under which injury or disease is caused. It tackles the question: does the agent cause the adverse effect? Information on adverse effects can be found in a variety of studies, including animal toxicology or bioassay studies, *in vitro* studies, structure–activity relationships, epidemiology, human clinical studies, and human volunteer studies (Table 21.4).

Hazard identification may also involve characterization of the disposition of a substance within the body and the interactions it undergoes with the body and with organs, cells, or even cell components. Such data may be valuable in answering the ultimate question of whether the types of toxic effects known to be induced by a substance under experimental conditions or in one population group (children, elderly persons, etc.) are also likely to be induced in humans as a whole. Hazard identification can be considered as a qualitative risk assessment, i.e., it determines whether and to what degree it is scientifically correct to infer that toxic effects observed in one setting will also occur in other settings. For example, are substances found to be carcinogenic or teratogenic in experimental animals likely to have the same effects in humans?

Of the over 300 substances, industrial processes, and complex mixtures ranked by the International Agency for Research on Cancer (IARC), approximately 39 chemicals and chemical processes have been categorized as carcinogenic to humans, while for another 25 or so there is limited evidence of carcinogenicity to humans. All known human carcinogens ranked by IARC have proved to be capable of inducing cancers in some (but not all) species of experimental animals, with the exception of arsenic. It has been suggested that arsenic may not have been adequately tested as yet. Thus, it is prudent to use the results of cancer bioassays as an important element in hazard identification.

Table 21.3 Information used in health risk assessment

I	Hazard identification	
	A	Human data
		Monitoring and surveillance
		Epidemiological studies
		Clinical studies
	B	Animal data
	C	In vitro data
	D	Structure-activity relationships
II	Hazard characterization (dose–response assessment)	
	A	Human studies
		Epidemiological studies
		Clinical studies
	B	Animal studies
		Minimal effects determination
		Dose–response modeling
		Special issues, including interspecies conversion and high-to-low-dose extrapolation
	C	Pharmacokinetic studies based on physiology
III	Exposure characterization	
	A	Demographic information
	B	Ecological analyses
	C	Monitoring and surveillance systems
		Animals
		Humans
	D	Biological monitoring of high-risk individuals
	E	Disposition and transport modeling (mathematical)
	F	Integrated exposure assessments
		Over time
		Over hazard (synergism)
IV	Risk determination	
	A	Mathematical
		Unit and population risk estimates
		Threshold determination (e.g., safety factor approach, NOAEL)
	B	Formal decision analysis
	C	Inter-risk comparisons
	D	Qualitative panel reviews
	E	Quantitative informal scientific advice
	F	Risk-benefit analysis

Source: US Department of Health and Human Services, 1986.

21.4.2 Dose–response assessment

Dose–response assessment answers the question: what is the relationship between the dose of a substance and the incidence of adverse effects of it in animals and subsequently in humans? It requires describing the quantitative relationship between the amount of exposure to a substance and the extent of toxic injury or disease. Data are obtained from animal studies or from studies in exposed human populations. The latter are preferred, but not always available. There may be a different dose–response relationship for each endpoint of a substance if it induces different toxic effects (e.g., cancer, birth defects) or when the conditions of exposure are different (e.g., single compared with repeated exposures) (Table 21.5).

The biologically effective dose or the concentration of a toxic substance at the target organ can be determined from pharmacokinetic or toxicokinetic studies. Such studies can

Table 21.4 Elements to consider in hazard identification

Animal bioassay data
What are the most common data available?
Assume that results from animal experiments are applicable to humans.
Epidemiological data
What is the association between exposure to a substance and disease?
Risk is often low, number of people exposed is small, latency period is long, and exposures are mixed and multiple.
Structure–activity relationships
What chemicals are known to cause adverse health effects?
What substances are structurally related and/or have similar mechanisms of toxicity?

Table 21.5 Dose–response assessment

Define the relationship between dose and response.
In general, as the dose of many toxicants increases, toxicity increases; however, the manner in which toxicity increases varies.
It is customary to extrapolate from the high doses administered to animals to low doses experienced by humans.
The validity of these extrapolations must be considered, and the statistical and biological uncertainties defined.

be carried out using simulations of rates of absorption, distribution, biotransformation, accumulation, and excretion of administered agents. These physiologically based pharmacokinetic (PBPK) models use actual blood flow rates to organs and biochemical reaction rates for major physiological systems to estimate the delivered dose to a target tissue and to predict effects in humans qualitatively or even quantitatively from data on experimental animals (see Part 3, Chapter 18). Such predictions assume that the target tissues in different species have the same types of responses. Such models potentially reduce the need for relying on assumptions and uncertainty associated with the purely statistical models of dose–response relationships.

Dose–response evaluation generally requires two extrapolations: one for species differences in body size, lifespan, and basal metabolic rate, and one for differences in doses between animal experiments (high doses) and human studies (lower doses to which humans are likely to be exposed). The dose–response assessment should describe and justify the methods of extrapolation used to predict incidence and should characterize the statistical and biological uncertainties in these methods.

21.4.3 Human exposure assessment

Exposure assessment answers the question: what exposures are currently experienced (actual exposure of people) or anticipated under different conditions (potential exposure)? It requires determining the amount or concentration of a substance to which humans are exposed, the nature and size of the population exposed to the substance, and the duration of exposure (Table 21.6). Exposure assessment has been defined as determining what the actual contact is likely to be with a chemical or physical agent. The magnitude of exposure is the amount or concentration of the agent available at the human exchange boundaries (skin, lungs, gut) during a specified time. The evaluation could concern past or current exposures or exposures anticipated in the future. The exposure assessment should describe and justify the methods of measurement as well as characterize the assumptions and uncertainties associated with the exposed population.

Table 21.6 Exposure assessment

What is the concentration or quantity of chemical or substance to which humans are exposed?
Over how long a period of time does exposure occur?
Identify the populations exposed to the chemical or substance.
Use analytical measurements or estimates of concentrations, monitoring data, and mathematical models to estimate exposures.

Exposure is the critical connection between potentially harmful factors (substances, trace elements, microbes) and human health effects. It is usually difficult to measure, because substances are often present in very low concentrations, move unevenly through several environmental pathways, persist for varying periods of time, and are absorbed by humans in varying amounts depending on individual characteristics such as age, behavior, and nutrition. The types of information used in exposure assessment are listed in Tables 21.6 and 21.7, all of which are aimed at questions such as: how do people become exposed? How can information be obtained on whether they have been exposed? What happens after exposure? What are the implications for public policy or further research?

For substances such as aflatoxin, a toxin produced by strains of the fungus *Aspergillus flavus*, the human populations with potential exposure would be all individuals who consume aflatoxin-contaminated food, such as peanuts and peanut products, rice, cereal, and corn. Because not all individuals in the population of interest will be exposed to identical doses, the assessment should attempt to understand the distribution of the dose in the population.

21.4.4 Risk characterization

Risk characterization generally requires integration of the data and analysis of the first three elements of risk assessment to determine whether and to what extent humans will experience any of the various types of toxicity associated with exposure to a substance (Table 21.7).

Risk characterization deals with the question: what is the estimated incidence and severity of the adverse effect? It is in characterizing the risks that the major assumptions, scientific judgments, and uncertainties should be identified so that the risk estimate can be better understood. In Europe, the term risk estimation is used to characterize risk. Many uncertainties exist, and several approaches have been suggested to improve the characterization and understanding of risks. The US Environmental Protection Agency (US EPA) has considered guidelines for risk characterization. Such guidelines could include, for example, the use of sensitivity analysis on data sets employed in risk extrapolation, expressing variability in risks from a given extrapolation model, statistical levels used to project risks (e.g., median, 95th percentile, range), and ways to evaluate risks quantitatively when the qualitative weight of evidence is low.

21.4.4.1 Limitations and assumptions in risk assessment

Risk assessment is a process that provides a framework for evaluating information and presenting that information in a form useful to decision makers. Risk assessment, however, is limited by:

Table 21.7 Risk characterization

Combine and integrate exposure and dose–response assessment.
Estimate quantitatively some measure of risk.
Identify major assumptions, scientific judgments, and estimates of uncertainties.

– lack of data on substances and adverse health effects;
– uncertainty about the cause of disease;
– uncertainty in extrapolating human risk from animal data.

These limitations have resulted in applying a set of assumptions, or default positions. The assumptions and uncertainties that abound in the risk assessment process have generated much controversy. When there is uncertainty or a lack of data, public health officials tend to use assumptions that will not underestimate risk. Nine of the most generally agreed-upon assumptions in risk assessment have been emphasized, although many more have been identified:

1. In the absence of adequate human data, adverse effects in experimental animals are regarded as indicative of adverse effects in humans.
2. Dose–response models can be extrapolated outside the range of experimental observations to yield estimates or estimated upper bounds on low-dose risk.
3. Observed experimental results can be extrapolated from one species to the other.
4. No threshold doses (i.e., doses below which no adverse effects will occur) exist for carcinogenesis, although threshold levels may apply for other toxicological outcomes.
5. Average doses give a reasonable measure of exposure when dose rates are not constant over time.
6. In the absence of toxicokinetic data, the effective or target dose is assumed to be proportional to the administered dose.
7. The risks from multiple exposure and multiple sources of exposure to the same chemical are usually assumed to be additive.
8. Regardless of the route of exposure (dermal, oral, or inhalatory), 100% absorption across species is assumed in the absence of specific evidence to the contrary.
9. Results associated with a specific route of exposure are potentially relevant for other routes of exposure.

21.4.4.2 Cancer vs. non-cancer risk assessment

The risks from a substance cannot be ascertained with any degree of confidence unless dose–response relationships are quantified. In the US, the regulatory distinction between substances that cause cancer and those that do not has a major impact on the extrapolation methods used to characterize the dose–response curve in the non-observable low-dose range. All carcinogens, whether characterized as genotoxic or non-genotoxic, are considered by US regulatory agencies to pose a risk, no matter how finite, at all doses, while for non-carcinogens a threshold dose is assumed. As will be discussed in the following sections, this distinction results in a different characterization for these two classes of substances. Most European regulatory agencies, by contrast, distinguish between carcinogens characterized as genotoxic and non-genotoxic. For genotoxic carcinogens, it is assumed that there is no threshold. For non-genotoxic carcinogens, the existence of a threshold is assumed, provided the mechanism of carcinogenesis is understood. JECFA has indicated that carcinogens vary in the degree of risk they represent, and the intentional use of a food additive known to be a carcinogen should be considered only under very restricted circumstances.

21.4.4.3 Characterization of non-cancer risks

For noncarcinogens, a threshold dose or level of exposure is assumed below which no effect is observed (Table 21.8). The dose–response evaluation requires estimation of the threshold dose and determination of the no-observed-adverse-effect level (NOAEL) from

observations in experimental animals or exposed people. The acceptable daily intake (ADI) (also called the tolerable daily intake, or TDI, see also Chapters 16 and 17) is estimated by dividing the NOAEL by a safety or uncertainty factor. Scientific guidelines and recommendations on the development and use of ADIs have been adopted by the Joint FAO/WHO Food Standards Program (Codex Alimentarius Committee on Food Additives), the FAO Committee on Pesticide Residues, and the WHO Expert Committee on Pesticide Residues. If the maximum daily intake of a non-carcinogenic substance is estimated to be lower than the ADI, then no risk is assumed for almost all members of the general population. Critical to this estimate, however, is the magnitude of the safety or uncertainty factor, which can range from 10 to 10,000 based on the data and on the policy of different regulatory organizations. For example, for non-nutrient substances, the Center for Food Safety and Applied Nutrition at the US Food and Drug Administration (US FDA) uses safety factors of between 100 and 2000, depending on the availability and type of data for analysis. The safety factor accounts for uncertainties concerning interspecies and intraspecies variation.

Where the WHO uses tolerable daily intake instead of accepted daily intake, the US EPA uses reference dose (RfD) to avoid the value judgment implicit in the calculation of an acceptable dose. The no-observed-adverse-effect level (NOAEL) and/or the lowest-observed-adverse-effect level (LOAEL) (Lowest found concentration or amount of a substance, which causes an adverse effect) are determined for each study and type of effect. To determine the RfD, uncertainty factors are applied to the NOAEL (or LOAEL if a NOAEL has not been established).

21.4.4.4 Characterization of cancer risks

From a scientific standpoint, substantial progress has been and is being made in understanding the mechanisms of toxicity, including carcinogenesis, and the causal relationships on which safety assessments are based. It is recognized to an increasing extent that "carcinogen" is difficult to define and that distinctions can be made among carcinogens based on the differing underlying mechanisms. Some substances initiate cancer directly and others are only involved secondarily in carcinogenesis. Thus for some carcinogens, as for non-carcinogens, there may be levels of exposure for which the possibility of harm to humans can be ruled out with reasonable certainty, a threshold dose determined, and for which instead a safety-factor or uncertainty-factor evaluation may be appropriate. A scheme for determining how chemical carcinogens could be identified is presented in Figure 21.2.

In the US, however, under Section 409 of the Food, Drug and Cosmetic Act, the Delaney Clause prohibits the use of food additives found to induce cancer in animals or humans.

Table 21.8 Characterization of risks

Non-carcinogens
For food additives, the no-observed-adverse-effect level (NOAEL) is divided by a safety or uncertainty factor to estimate an acceptable daily intake (ADI).
For systemic toxicants, US EPA developed the reference dose (RfD) approach, where the NOAEL is divided by an uncertainty factor and a modifying factor. Generally, the RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of harmful effects during a lifetime.
Genotoxic carcinogens
Risk is estimated from the cumulative dose and/or the dose–response curve extrapolation.
Mathematical models are used to extrapolate to low–dose response.
A range of risks might be produced using different models and assumptions about dose–response curves, relative sensitivities of humans and animals, and for different estimates of human doses.

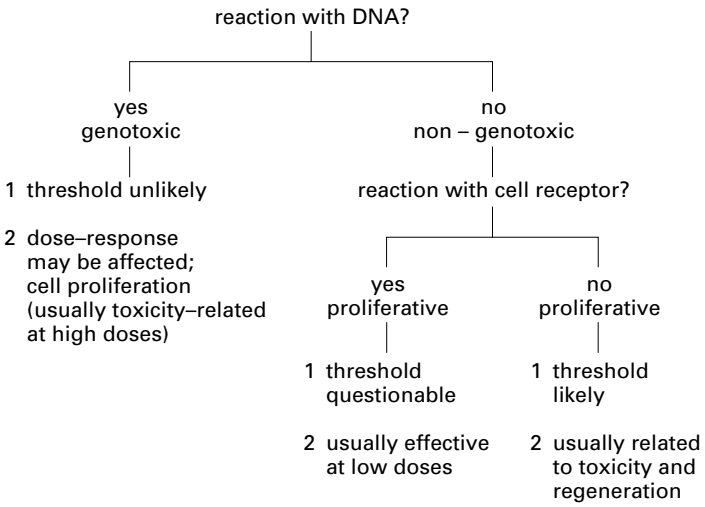

Figure 21.2 Proposed scheme for classification. Source: Cohen and Ellwein, 1990. With permission.

In contrast to the general safety standard for non-carcinogens, which recognizes the impossibility of assessing the complete absence of risk, the Delaney Clause has been interpreted as taking a zero risk approach to substances implicated as carcinogens. It should be stressed that this clause was enacted during a period when relatively few carcinogens had been identified and even fewer were believed to be present or associated with food. The result in the US was the assumption that there was no threshold dose for carcinogens and that oncogenic risk was a function of the cumulative lifetime dose (Table 21.8).

The non-nutritive sweetener saccharin has been shown to induce bladder cancer in rats. It is not metabolically activated when ingested by humans or animals, does not react with DNA, and is not mutagenic in short-term tests. Therefore, it is considered non-genotoxic. The lowest dose for an effect in rats is 2.5% sodium saccharin in the diet, while there is no effect with acid saccharin at 7.5% in the diet. The NOAEL in rats is 1.0% in the diet; there is no effect in the animals if the urine is acidified. At higher doses, increased cell proliferation of the adult rat bladder epithelium is observed. Urinary silicate precipitates and/or microcrystals are critical phenomena in the development of the lesions in rats. There is no evidence of any interaction of saccharin with cell receptors; relatively high doses are required for the effect in the bladder. Thus, as suggested in Figure 21.2, the proliferative response is probably related to toxicity and cellular regeneration, and a threshold dose is likely for this effect.

21.4.4.5 Characterization of risk using mathematical modeling

As most of the information on whether a substance is capable of inducing cancer is obtained from animal studies at high doses, statisticians developed mathematical models to extrapolate from these high-dose level studies to determine the risk at the low doses to which humans would be potentially exposed. This modeling process is used for quantitative risk assessment of chemical carcinogens and involves eight steps (Table 21.9). It has been termed an *empirical risk assessment model* or *default carcinogen risk assessment methodology*. Starting with carcinogenicity in the rodent bioassay, the procedures and calculations are outlined to reach the exposure analysis and risk-benefit analysis needed to determine exposure levels and cancer risks that society can tolerate.

Table 21.9 Empirical risk assessment model or default carcinogenic risk assessment methodology

1. Positive response in rodent bioassay
2. Appropriate dose measure; typically mg/kg body weight per day
3. Dose–response function selected for risk to rodents; typically linearized multi-stage model
4. Estimate of the variability of the dose–response function; typically 95% confidence interval
5. Linearized upper 95% bound on risk in the 1 in 10^{-6} region selected to determine quantitative value for risk assessment for rodents
6. Interspecies extrapolation to estimate risk for humans in dose-region of interest
7. Extrapolation from one exposure route to the other
8. Exposure analysis and risk benefit analysis to determine exposure levels and risks society can tolerate

The modeling and extrapolation processes employed in quantitative risk assessment are considered by many to be the most important sources of uncertainty in the risk assessment process. A quantitative estimate of the risk from a substance at a particular low-dose level is highly dependent on the mathematical form of the presumed dose–response relationship. Differences between models of at least three to five orders of magnitude are not uncommon. One difficulty with low-dose extrapolation is that some methods fit the data from animal experiments reasonably well, and it is impossible to distinguish their validity on the basis of a good fit. From a mathematical point of view, distinguishing between the models on the basis of their fit with experimental data would require an extremely large experiment which, from a practical point of view, is probably impossible. The different approaches used by the various regulatory agencies for assessing risk are, for example, reflected in the acceptable exposure levels set for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Table 21.10). Not all agencies assume that no threshold exists for carcinogenesis. Although TCDD has proved to be extremely toxic to some rodents, its carcinogenic potential to humans has been the subject of considerable scientific controversy. TCDD has also been shown to induce a wide spectrum of adverse effects, not only carcinogenicity, in experimental animals. Use of the NOAEL and a general safety standard as well as a cancer dose-modeling approach yields a 2,000-fold range of allowable exposure levels by various regulatory agencies (Table 21.10).

21.5 Characterization and communication of risks

The importance of the risk characterization step is reflected by the distinction between cancer and non-cancer risks. The interpretation of the concept "one in a million risk of cancer" is often the basis of regulatory decisions in the US. Substances with cancer risks estimated to be greater than one in a million are generally not approved at the federal level.

In 1987 the commissioner of the FDA explained the concept of one in a million risk of cancer when he discussed the cancer risk from residues of methylene chloride residues, a solvent used to decaffeinate coffee: "The risk of one in a million is often misunderstood by the public and the media. It is not an actual risk, i.e., it is not expected that one out of every million people will get cancer if they drink decaffeinated coffee. Rather, it is a *mathematical* risk, based on scientific assumptions used in risk assessment. When the FDA uses the risk level of one in a million, it is confident that the risk to humans is virtually nonexistent."

Thus, how a risk is characterized and by whom can make a significant impact on how the risk assessment of a substance is interpreted and received. These aspects of perception and communication are discussed in Part 3, Chapter 22.

Table 21.10 Acceptable daily intakes of TCDD proposed or adopted by various regulatory agencies

Agency	Dose-response extrapolation	Allowable intake (fg/kg/day)
US EPA	Linearized multi-stage	6.4
CDC[b]	Linearized multi-stage	28–1,428
OME[c]	Safety factor (100)	10,000
SINH[d]	Safety factor (250)	4,000
FEA[e]	Safety factor (100–1000)	1,000–10,000
FDA[f]	Safety factor (77)	13,000
NYSDH[g]	Safety factor (500)	2,000

[a] US Environmental Protection Agency
[b] US Centers for Disease Control
[c] Ontario Ministry of Environment, Canada
[d] State Institute of National Health, The Netherlands
[e] Federal Environmental Agency, Germany
[f] US Food and Drug Administration
[g] New York State Department of Health
Source: Paustenbach, 1989. With permission.

21.6 Risk Evaluation/Risk Management

Risk assessments have many uses, but a major one is to assist decision makers with the complex choices regarding the options in managing or reducing the potential human health risks associated with a substance or product. *Risk management* is defined in the US as the process of evaluating alternative regulatory actions and selecting among them. It has been characterized as an agency decision-making process that entails consideration of political, social, economic, and engineering information along with risk-related information to develop, analyze, and compare regulatory options and to select the appropriate regulatory response to a potential chronic health hazard. The European Union and WHO use the term *risk evaluation*, defined as a process of analysis that takes into account value systems that cannot be measured in ways described for risk estimation. Risk evaluation relies on social and political judgment, and is aimed at determining the importance of hazards and the risk of harm from the point of view of communities and individuals facing that risk. It is the decision maker or risk manager who must be able to compare risks, risk trade-offs, and risks with the potential benefits of using the material. A series of questions that can be posed regarding risk management are compiled in Table 21.11. These questions were developed in a publication by the US Government Accounting office in Health Risk Analysis. Using experience and judgment, the manager must determine a level of risk that is acceptable.

21.7 Summary

Interspecies extrapolation as well as *high-to-low dose extrapolation* play a major role in estimating health risks associated with exposure to chemicals. The qualitative or quantitative characterization of a risk also has a major impact on the risk assessment. Issues in risk characterization are important in both the assessment and the management processes. Throughout the risk management process, regardless of the agency, decisions affecting risk and safety are made in varying degrees of uncertainty. The *risk assessment/risk management*

Table 21.11 Development of risk management options

Were the variables or factors such as costs and benefits associated with each option specified?
Were the methods and assumptions used in the development of such variables as costs and benefits specified?
Were value judgments for each risk management option specified?
Were uncertainties associated with the development of each risk management option specified?
Did the agency use an analytical approach other than or in addition to worst-case analysis?
Were the risk management options compared with earlier risk management options for similar hazards as a validation check?
Was the development of risk management options independent of the risk assessment work?
Were the risk management options reviewed with respect to practicality?
Was the achievable risk reduction estimated for each option?
Were both population and individual risk indicators examined?
Was the relationship between risk reduction and cost examined for each option?

Source: US Government Accounting Office, 1991.

paradigm is a critical and useful tool, providing a framework in which to *harmonize* complex and diverse *scientific regulatory issues* and attempt consistency in them. As *global harmonization of risk issues* continues to evolve, it will be increasingly important for the scientific community to understand these issues and communicate effectively about them.

21.8 Epilogue

Since the preparation of this chapter, risk analysis has become an increasingly visible and controversial topic in the United States. The discussion has centered on sweeping legislative reform proposed during the 104th Congress (1995-1996) and included suggested reforms in *risk assessment*, *risk management*, and *risk communication*. Omnibus risk/*regulatory reform* legislation, which in some cases would supersede existing law, has been proposed, as well as reforms of specific legislation, including the Safe Drinking Water Act, the Comprehensive Environmental Remediation and Cost Liability Act (Superfund), and the Federal Food, Drug & Cosmetic Act (FFDCA, and specifically the *Delaney Clause*). While none of these measures have been passed into law, the discussions are likely to be on-going for several years, but already have had impacts on agency approaches and policies.

Key issues identified from these complex discussions include *risk*- and *cost-benefit analysis*, *risk characterization* policy, peer review policy, priority setting policy for agencies, relationship between individual statutes and "supermandate" provisions which could supersede individual statutes; and provisions for judicial review of agency actions.

Some selected examples of how these issues translate into legislative language are illustrated by the following, which have appeared somewhat consistently in many of the proposed bills:

- risk assessments based on the most "scientifically objective and unbiased information;"
- risk characterizations to state the "reasonable range of scientific uncertainties" and, in addition use the "best estimate" of risk, and the "plausible upper-bound or conservative estimates in conjunction with plausible lower bound estimate;"

- comparison of risks to establish priorities for allocation of resources for risk reduction activities;
- establishment of peer review programs that "shall not exclude peer reviewers with substantial and relevant expertise" because they represent entities "that may have a potential interest in the outcome" of the peer review, though full disclosure of such interests may be mandated;
- for major rules ($50-100 million), benefits of the rule must "justify" the costs; if the statutory basis for the rule prohibits the cost-benefits balancing, the "least net cost" option among reasonable alternatives must be adopted;
- judicial review of agency actions and compliance with the law;

This intense attention to risk reform by the 104th Congress follows the actions of the 103rd Congress which mandated, under the Federal Crop Insurance Reform and Department of Agriculture Reorganization Act of 1994, the creation of an Office of Risk Assessment and Cost Benefit Analysis. The office has responsibility to assess risks to human health and the environment and prepare cost-benefit analyses for proposed "major" regulations—those having an impact on the economy of $100 million of more.

It has also been suggested that the current debate over *regulatory reform* and risk assessment overlooks the *public health* perspective. Whereas much of what is in the regulatory arena is based on the premise of public health protection, the ongoing arguments over *risk reform* may not translate into public health protection. The Centers for Disease Control, which has major responsibility for *public health protection* and disease prevention, has been virtually absent from the discussions over *risk reform legislation*. To increase understanding and communication about risk analysis among diverse audiences, senior federal agency representatives drafted a set of principles for using risk analysis that could be adopted by agencies on an individual basis. The principles identify terms and briefly describe the elements that comprise risk assessment, risk management, risk communication, and priority setting using risk analysis.

Much of the pending environmental and regulatory reform legislation have requirements that have to be met by state health and environment departments, which lack the tools necessary for performing the proposed enhanced risk assessment and cost-benefit analyses. While states have the capacity for the present framework, some of the pending legislation would require significant and probably costly changes to current state procedures.

During 1995-1996, the *President's Commission on Risk Assessment and Risk Management* held hearings across the United States from a variety of experts and the public. The bipartisan commission was established under the Clean Air Act (CAA) Amendments of 1990, following an earlier period of intense debate over "residual risk," the risk levels remaining after the CAA technology-based standards have been implemented. The commission's report is expected during 1996 and would have jurisdiction and impact on all federal risk assessment and risk management policies, not just those associated with air emissions and contaminants.

Changes in the food safety and inspection practices have been or are being proposed at both the United States Department of Agriculture *(USDA)* and the Food and Drug Administration *(FDA)*. The Department of Agriculture has proposed a "paradigm" shift in the way meat and poultry products are inspected. The USDA's *Food Safety and Inspection Service* is pursuing a strategy that over time will improve the safety of meat and poultry products and significantly reduce the risk of *food-borne illness*. The strategy relies upon the Hazard Analysis Critical Control Point *(HACCP)* inspection system, which focuses on prevention of infectious agent contamination and on mandating microbial testing to detect the presence of pathogens. A similar approach using HACCP has been proposed by the FDA to apply to seafood to increase the safety of the seafood supply.

More recently, the United States Environmental Protection Agency released in the Federal Register new Proposed *Guidelines for Carcinogen Risk Assessment*. These proposed guidelines update the 1986 guidelines and are intended to allow incorporation of the increasing knowledge of the mode of action of cancer formation and the uncertainties associated with not only whether a chemical causes cancer in humans, but how it might do so. Other EPA related activities at various stages of preparation include guidelines on *Ecological Risk Assessment*, Exposure Assessment, Non-cancer Risk Assessment, *Benchmark Dose*, and *Endocrine Disruptors*. While this approach to consideration of *carcinogenicity mechanisms* has received much attention in the United States during the last several years, it is already in use in various forms in Western European countries and in The Netherlands since 1978.

And finally, numerous scholarly studies have been released and published on topics touched on in this chapter, most notably by the National Research Council on carcinogens and *anticarcinogens* in the human *diet* and the means by which cancer risks associated with food intake and the diet are estimated. The diet in the United States contains both naturally occurring and synthetic substances that are known or suspected to affect cancer risk. It has been suggested from such studies that toxic chemicals that occur naturally in foods may pose a greater-though still small-risk of cancer than the residues of synthetic pesticides that people consume in their diets.

Thus, the *risk paradigm* in the United States is under vigorous scrutiny from the scientific community, the regulatory community, decision-makers, and the public. In response to this scrutiny, federal and state agencies with responsibility for protection of the public health and environment, and which use risk analysis as a tool to fulfill their responsibilities, have implemented major changes and reforms. The success of these reforms will require several years to be measured.

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