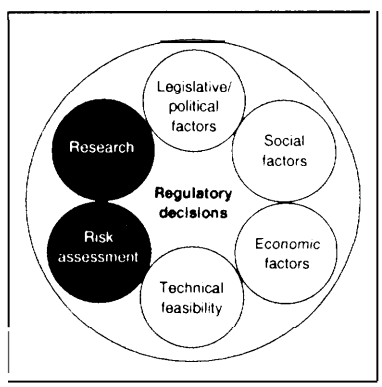
An Introduction to Health Risk Assessment and Its Research Base

2

This chapter presents a brief introduction to the process of health risk assessment, the kinds of research and data that support it, and the controversies that have arisen in some areas of research and assessment. It is intended for the lay reader with little or no technical background. Because of its brevity, it cannot provide details about specific differences in the use of health risk assessment among the Federal agencies or a thorough review of the scientific literature. Readers interested in pursuing those topics are advised to look at recent, accessible reviews (Paustenbach, 1989a, 1989c; Rosenthal et al., 1992; Silbergeld, 1993; Zimmerman, 1990). The chapter does include a brief discussion of the costs of regulatory compliance and of treating environmentally related diseases.

Health risk assessment is most developed for estimating the risk to humans from exposure to carcinogens (box 2-A). Therefore, this chapter and, indeed, this report tend to focus on carcinogens, not because substances causing other risks to health are less important but because Federal agencies have more experience in assessing the risk of cancer. The report also emphasizes risk assessment associated with low levels of exposure to harmful substances in the environment, probably the area of greatest scientific controversy.



We estimate risks every day, every time we cross the street, every time we drive. Before making a left turn, we examine the hazard (the oncoming traffic), we consider the consequences of exposure to the hazard (dents, injuries, death), and we estimate the probability of occurrence (the likelihood of being hit). When we overestimate that probability, we hesitate and waste time. Usually, we assess the risks reasonably well, turn when the

Box 2-A—The Growth of Health Risk Assessment in the Federal Government

Although the connection between the environment and human health was recognized in ancient times, attempts to quantify that relationship are of more recent origins. Scientific papers published in the early 20th century described unusual diseases observed in workplaces, and by the 1930s, researchers were able to estimate quantitative relationships between occupational exposure to potentially hazardous substances and their effects on human health. One observer refers to the early use of these relationships to establish no-observed-effect levels (NOELs) for humans as "a primitive quantitative risk assessment methodology" (Friess, 1987). By the 1950s, research on safety factors (later known as uncertainty factors) was developing as well.

But using NOELs and uncertainty factors for quantifying the risks associated with carcinogens became increasingly problematic. Studies showed that even very low levels of ionizing radiation or certain chemicals seemed to cause corresponding low levels of disease, but thresholds could not be established. Researchers thus began to develop dose-response extrapolation models starting in the 1960s to estimate the effects on humans of low doses of carcinogens.

The Nuclear Regulatory Commission was probably the first government agency to use such models to estimate the risks to humans associated with ionizing radiation. The Food and Drug Administration (FDA), however, was the first Federal agency to employ those quantitative methods in a regulatory context. In 1973, FDA proposed using an extrapolation model to determine the level of sensitivity necessary for methods to detect residues in foods from drugs given to animals. Since then, the use of health risk assessment has spread to other agencies within the Department of Health and Human Services, such as the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry.

In the early 1970s, the Environmental Protection Agency (EPA) sought to suspend the registrations of pesticides that had been shown to be carcinogenic in animal tests. After being criticized for taking what some viewed as a zero-risk approach, EPA responded by developing comprehensive guidelines for assessing the risks associated with health effects other than cancer. Today, programs throughout EPA use health risk assessment.

The Occupational Safety and Health Administration (OSHA) proposed its generic cancer policy in 1977 and formally adopted it in 1980, despite intense criticism from the regulated community. But a 1980 U.S. Supreme Court decision on OSHA's benzene regulation forced the agency to make significant changes in its policy. Today, OSHA can use studies by the National Institute for Occupational Safety and Health to meet the Court's requirement of showing that an exposure poses a significant risk that would be reduced by imposing a regulation. The Consumer Product Safety Commission (CPSC) also turned to the use of health risk assessment in the 1970s, publishing its guidelines in 1978. Still other agencies, such as the Departments of Defense and Energy, use risk assessment to help protect workers and the public from the risks associated with their activities. These agencies, however, do not use risk assessment in a regulatory context.

Attempts to coordinate policy across the Federal agencies also began in the 1970s, particularly through the efforts of the Interagency Regulatory Liaison Group, formed in 1977 by agreement of the four main regulatory agencies: CPSC, EPA, FDA, and OSHA. The groups published a draft of a report on cancer policy in 1979. in the same year, the White House Office of Science and Technology Policy (OSTP) published another set of cancer guidelines. OSTP has continued its efforts to coordinate the use of health risk assessment across Federal agencies, publishing further cancer principles in 1985,

In short, health risk assessment is a relatively young method of analyzing data on toxic substances. As its use has grown since it was introduced into regulatory programs in the 1970s, it has been adapted to suit the needs of many agencies and programs. Since the late 1970s, efforts have been made that continue to this day to coordinate the use of health risk assessment across agencies.

SOURCES: S. Friess, "History of Risk Assessment," *Pharmacokinetics in Risk Assessment: Drinking Water and Health, vol. 8* (Washington, DC: National Academy Press, 1987); P.B. Hutt, "Use of Quantitative Risk Assessment in Regulatory Decisionmaking Under Federal Health and Safety Statutes," *Risk Quantitation and Regulatory Policy,* Banbury Report 19, D.G. Heel, R.A. Merrill, and F.P. Perera (eds.) (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1985) D.J. Paustenbach, "A Survey of Health Risk Assessment," *The Risk of Environmental and Human Health Hazard%,* DJ. Paustenbach (cd.) (New York: John Wiley & Sons, Inc., 1989); M.E. Rushefsky, Making *Cancer Policy* (Albany, NY: State University of New York Press, 1986).

probability of an accident is small, and make it safely through the intersection. Occasionally, however, we underestimate the probability of being hit and sometimes suffer the consequences.

Risk assessment uses similar thinking to determine the probability of harm or disasters—both natural ones, like fires and floods, and those resulting from engineering problems, like engine failure in aircraft, or from exposures to toxicants. This information is useful for those who work to prevent disasters-for example, the engineers who design safety features-and for those who insure potential disaster victims. It is also useful for governments, which seek to protect the health and safety of their citizens, and, ultimately, for citizens themselves, who participate in decisions about acceptable or tolerable and unacceptable or intolerable levels of risk.

Health risk assessment deals with the risks people face when they are exposed to harmful substances. It is generally used for agents whose health effects are hard to measure directly, such as low levels of exposure to chemicals and ionizing radiation. Time factors may also increase the difficulties involved in measurements. Diseases resulting from exposure to some harmful substances, like asbestos, may not develop for 20 or 30 years. And some substances, like lead, have no obvious acute effects at low levels but can cause subtle and significant effects after chronic low-level exposure.

In such situations, questions arise not only about the probability of occurrence but also about the relationships between the duration and intensity of the exposure to the hazard and the type and severity of the adverse health effect. Researchers have directed most of their efforts in developing health risk assessment toward answering the following questions: What health effects are associated with exposure to a particular substance? How large a dose—and at what frequency and over how long a period of time-does it take to cause those effects? How much of a substance are people likely to be exposed to? Given some level of exposure, how many people may be affected?

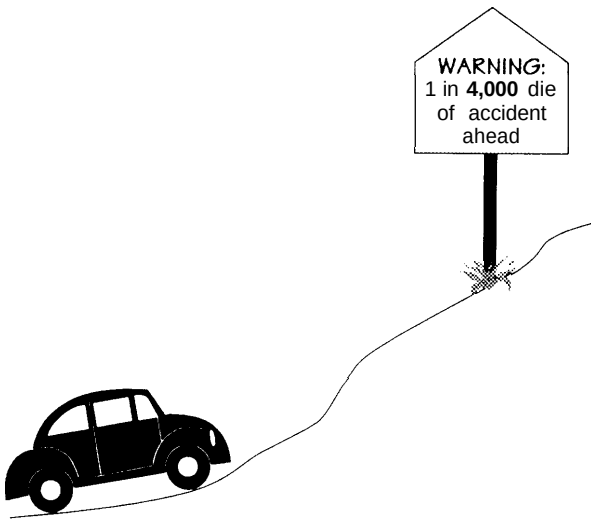
Table 2-l—Estimated Risk of Death From Various Human-Caused and Natural Accidents

Accident	Risk
Automobile	1 in 4,000
Drowning	1 in 30,000
Air travel	1 in 100,000
Lightning	1 in 2 million

SOURCE: C.D. Klassen, "Principles of Toxicology," *Casarett and Doull's Toxicology,* C.D. Klassen, M.O. Amdur, and J. Doull (eds.) (New York, NY: Macmillan, 1986).

Health risk assessment provides a systematic approach to evaluating and quantifying risk. As it pertains to the health effects of toxic substances, risk is the probability of injury, disease, or death for individuals or populations who undertake certain activities or are exposed to hazardous substances. It is sometimes expressed numerically (e.g., 1 excess cancer death in 1 million exposed people). A risk of 1 in 10,000 may be described as 10^{-4}, a risk of 1 in 1 million as 10^{-6}, and a risk of 1 in 100 million as 10^{-8}. Risks smaller than 10^{-6} are rarely regulated (Rosenthal et al., 1992; Travis et al., 1987). If quantification is not possible or necessary, risk may be expressed in qualitative terms (e.g., low, medium, or high risk).

Experts have quantified the risk of death from some familiar hazards (table 2-l). Traveling in an automobile, for example, involves a risk of accidental death of 1 in 4,000 (i.e., people on the road), which is relatively high. As might be expected, the risk of being killed by lightning is much lower (1 in 2 million). But the public's perception of risk does not always agree with the risk calculated by experts. Some people, for example, avoid air travel even though the risk associated with automobile travel is 25 times greater. In particular, people tend to overestimate the risk or number of deaths from rare, dramatic events and underestimate the risk from common, undramatic causes. Public perception of the annual rates of death from floods or tornadoes are



typically overestimated, whereas the risks from smoking and drinking alcoholic beverages are typically underestimated.

In everyday life, we evaluate the risks associated with various activities and make choices, considering such factors as benefits, costs, convenience, and past experience. As a society, we must make similar choices. Health risk assessment can help clarify those decisions by illuminating the kinds of hazards that result from exposure to a substance, by identifying those people who have been exposed, and by estimating the magnitude of the risk associated with different levels of exposure. But health risk assessments are only one of the factors on which such decisions are based. Decisionmakers may also need to consider the technical and economic feasibility of various control technologies, social values and political forces, the missions of their agencies, and their legal responsibilities.

The results of a health risk assessment are usually intended for use by "risk managers,' decisionmakers who determine what, if anything, should be done to reduce or eliminate a risk (Zimmerman, 1990). Health risk assessment is used not only by agencies of the Federal Government, the main focus of this report, but also by other organizations with an interest in the health effects of exposure to chemicals. Those groups may include State and local authorities, environmentalists, manufacturers, representatives of consumer organizations, and, increasingly, local citizens.

Health risk assessment is used for many different purposes as well. People may be exposed to many types of potentially harmful substances through the air they breathe, the water they drink, and the food they eat. They may be exposed in the workplace, outdoors, or at home. Those exposures may be regulated under a variety of Federal and State laws. Consequently, the details of the health risk assessment process may vary, depending on those circumstances.

RESEARCH DATA FOR HEALTH RISK ASSESSMENT

The primary source of data for assessing human health risks is epidemiologic, toxicological, structure-activity relationship, and exposure studies. Other research data on metabolism, pharmacokinetics, and mechanisms of toxicity are used to determine the relevance of those primary data for predicting adverse health effects in humans. The primary sources of data are described briefly below.

Epidemiologic Studies

Epidemiologic studies examine patterns of disease in human populations and the factors that influence those patterns. The greatest advantage of such studies is their direct relevance to human populations because they are based on the experiences of human subjects. Epidemiologic studies are especially informative when levels of exposure are well documented, the exposed population is well defined, and the adverse effect associated with the substance is known. Those conditions, however, are seldom met.

The essence of epidemiology is the observation of a natural experiment-the release of an agent into an environment, resulting in exposure of a population. Sometimes, however, relationships

between exposure and health effects may be obscured because of a lack of precise information about the amount and frequency of exposure or the presence of confounding factors, such as exposure to other substances. Factors such as genetic variability and population mobility are difficult to take into account. In addition, most epidemiologic studies are not sensitive enough to detect small increases in risk. Still when enough information is available and epidemiologic studies can be undertaken, they can provide valuable information about the relationships between exposure to hazardous substances and human health.

Epidemiologic studies may be descriptive, observational, or experimental (Lilienfeld and Lilienfeld, 1980). Descriptive epidemiologic studies provide clues to the causes of disease by examining the distribution and extent of disease in different groups of people defined by age, race, gender, or other parameters. In observational studies, scientists examine statistical associations between exposure to a hazard and disease in individuals or relatively small groups. In experimental epidemiology, scientists control the population groups in the study, determining in advance the groups to be exposed, often in occupational or clinical settings.

Toxicological Studies

Most often, the information needed to predict adverse health outcomes from exposure to potentially hazardous chemicals comes from testing substances in animals or through in vitro tests, that is, in cells or tissues isolated from animals and humans. Such toxicological studies allow scientists to test chemicals and control the amount and conditions of exposure and the genetic variability of the subjects, factors that cannot be controlled in most epidemiologic studies. Toxicological studies are the only means available to evaluate the risks of new chemicals.

Biologically, animals, even the rats and mice typically used in toxicity testing, resemble humans in many ways. A substantial body of evidence indicates that results from animal studies can be used to infer hazards to human health (Huff, 1993; Huff and Rail, 1992; NRC, 1991a). There are exceptions to this generalization, but each must be proved before setting aside the assumption that animal tests are predictive. The proof can be data on human toxicity that convincingly contradict a specific finding in animals, or mechanistic or physiological reasons that support the idea that the animal data are irrelevant to humans. Otherwise, the assumption is generally made that toxicity data from animals can be used to identify potential human hazards (NRC, 1991a; Perera and Boffetta, 1988; Silbergeld, 1993; U.S. EPA, 1986a). Much of toxicological research focuses on developing and employing various animal ‘‘models’ to predict adverse health effects in humans, understand mechanisms of toxicity, and verify that metabolic pathways and toxic effects are similar in test animals and humans.

Toxicological disciplines can be distinguished by the “endpoint” being studied, that is, the resulting disease or the organ affected by exposure to a toxic substance. Increasingly, researchers are studying subtle endpoints other than cancer, such as immunotoxicity (U.S. Congress, OTA, 1991a), lung toxicity (U.S. Congress, OTA, 1991b), neurotoxicity (U.S. Congress, OTA, 1991c), reproductive and developmental toxicity, and liver and kidney toxicity. Scientists are also devoting more attention to studying the effects of long-term (’ ‘chronic’ exposures, rather than the effects of large, short-term (’‘acute’ exposures.[1]

Toxicological studies, however, have limitations. Cost considerations limit most animal

[1] For excellent reviews and research papers on the various types of toxicological studies being conducted on health effects other than cancer, see volume 100 of *Environmental Health Perspectives* (1993), in particular, see Luster and Rosenthal (1993), Schwetz and Harris (1993), and Fowler (1993).

studies to a few hundred test animals, and in most instances, researchers use high levels of exposure to increase the likelihood of observing a statistically significant effect in a relatively small group of animals. It can also be very difficult to verify any quantitative extrapolation of the results of animal studies to human effects.

Structure-Activity Relationships

Structure-activity relationships refer to studies that compare the chemical structures of substances in order to make inferences about toxicity and identify candidates for further testing. The accuracy of prediction from this method of assessment has grown over time, but it is clear that there are no simple relationships between structure and toxicity (Friess et al., 1986; Klopman and Rosenkranz, 1991; Rosenkranz and Klopman, 1989).

Exposure Data or Models

Data for assessing human exposure come from measuring the presence of an agent in air, water, soil, or food. Frequently, such data are not available for a specific kind or level of exposure. In those situations, mathematically derived computer models are used to simulate the exposure conditions and predict the level of possible exposures.

Personal monitoring measures the actual concentrations of a hazardous substance to which people are exposed by using devices that individuals wear or by sampling the food, air, and water they eat, breathe, and drink. Biological monitoring measures the toxicant or its metabolize in biological samples such as blood or urine. Ambient monitoring measures hazardous substances in air, water, or soil at freed locations. That method is often used to provide some information about the exposure of large populations, such as people exposed to air pollution in a region.

THE HEALTH RISK ASSESSMENT PROCESS

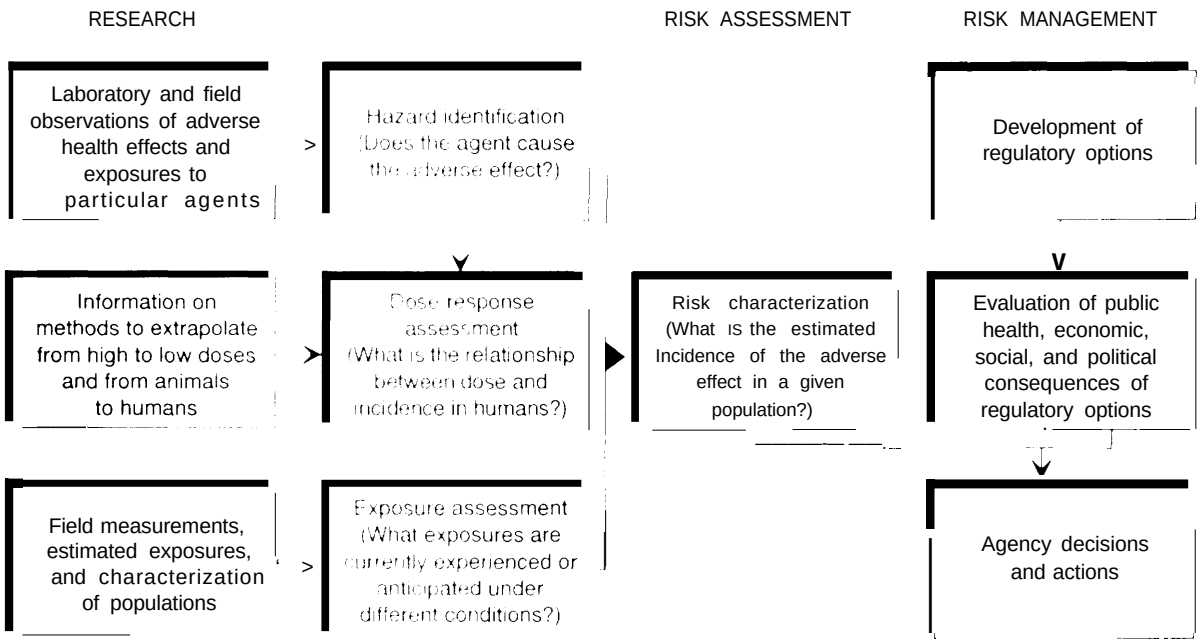
Health risk assessment uses tools derived from many scientific fields in a systematic way to organize and evaluate the available scientific information about a potentially harmful substance. The goal of health risk assessment is to identify the kinds of adverse health effects that may be associated with exposure to a harmful substance and to quantify the magnitude of the risk of experiencing those effects according to levels of exposure. As conducted by Federal agencies, health risk assessment consists of some or all of the following four steps: hazard identifi cation, dose-response evaluation, exposure assessment, and risk characterization (NRC, 1983; U.S. Congress, OTA, 1981; U.S. EPA, 1986a; U.S. OSTP, 1985). Originating in a 1983 National Research Council report, figure 2-1 is the most commonly used graphic representation of the risk assessment process.

Hazard Identification

Hazard identification evaluates the available data on the types of injury or disease that maybe associated with exposure to a substance and on the conditions of exposure under which the disease or injury maybe produced. For example, does a substance cause cancer or birth defects? Does it harm the nervous system or the immune system? Three types of scientific studies are used to identify adverse effects associated with exposure to chemicals: epidemiologic studies, toxicological studies, and structure-activity relationships (Cohrssen and Covello, 1989; Lave and Omenn, 1986; U.S. Congress, OTA, 1981; U.S. EPA, 1986a; U.S. OSTP, 1985).

Hazard identification involves judgments about the quality, relevance, and limitations of the available data. It typically includes an evaluation of all available toxicological data (much less frequently, an evaluation of all epidemiologic data) to identify those adverse effects that are best documented and those that are most relevant to

Figure 2-I—Relationship of Research, Risk Assessment, and Risk Management



SOURCE: National Research Council, *Risk Assessment* **In the** *Federal Government: Managing the Process* (Washington, DC: National Academy Press, 1983).

human health. Generally, the toxic effects causing the greatest concern are those that are the most severe, occur at the lowest levels, and persist after exposure ceases.

Dose-Response Assessment

In the second part of a health risk assessment, assessors determine the quantitative relationship between exposure to a substance usually expressed as a dose, and the incidence of disease. That relationship may be based on information from epidemiologic studies of exposed humans or tests on animals.

Only rarely, however, is information available on doses and responses in the range typical of human ''environmental'' exposure. More often, information derived from both epidemiologic and toxicity studies is based on far higher levels of exposure. Because for any given chemical and route of exposure, the severity and frequency of a biological response usually increase with the dose, it is necessary to estimate biological effects at the doses that people typically encounter, based on dose-response relationships. Currently, there are two main methods of using the high experimental doses to predict effects at the low doses of interest: one method for noncarcinogens and another for carcinogens. Such predictions of effects at low doses from the observed effects at high levels are termed extrapolations.

For noncarcinogens, biological effects are assumed to occur only when a certain level of exposure has been exceeded. That level is known as the threshold. Researchers usually derive an approximate threshold from identifying a‘ ‘no-observed-effect level’ (NOEL) or a “no-observed-adverse-effect level’ (NOAEL) in exposed people or experimental animals. The NOEL is that dose at or below which no biological effects of any type are detected; the NOAEL is that dose at or below which no harmful effects are detected. If scientists observe more than one effect in animal

tests, they generally use the effect occurring at the lowest dose in the most sensitive animal species and sex as the basis for estimating a NOEL or NOAEL. Safety factors or uncertainty factors (which are discussed further in the section on risk characterization) are used to account for uncertainties in the use of NOELs or NOAELs for determining g levels of acceptable exposure.

For carcinogens, researchers generally assume that there are no thresholds, that is, that carcinogens pose some risk at even the lowest levels of exposure. For those substances, extrapolations from high to low doses are done using mathematical models, and a number of those models fit data derived from toxicity tests fairly well; because such data are available only for high doses, the extrapolation models make quantitative predictions of risks at lower doses using different models, which can result in widely divergent predictions of risk. Because data are seldom available at those doses, those predictions can seldom be verified or falsified.

The most commonly used model among Federal agencies is the linearized, multistage model. It is based on the hypothesis that cancer develops in stages and that a carcinogen can have an effect at each stage (U.S. OSTP, 1985). Agencies use the model to estimate an upper limit to the increase in probability of cancer resulting from a given exposure, rather than a "most likely" or "best" estimate (U.S. EPA, 1986a).

When the dose-response relationship is based on animal data, yet another extrapolation is necessary. Researchers use species extrapolation factors, also called scaling factors, to account for differences between test animals and humans that may affect the response to exposure to harmful substances. Such factors can include considerations of lifespan, body size, genetic variability or population homogeneity, metabolic rate, and excretion patterns (Travis and White, 1988; U.S. OSTP, 1985).

Exposure Assessment

Exposure assessment determines or calculates the number and kinds of people exposed to a substance, the amount of the substance to which individuals or populations are exposed, and the distribution, sources, routes, frequency, and duration of exposures. Assessors then use this information to estimate the dose, that is, the amount of a substance that reaches the cells, tissues, or organs of people who have been exposed. In general, less information is available about actual human exposure than about other aspects of health risk assessment (Cohrssen and Covello, 1989; Paustenbach, 1989b). Paustenbach (1989b) states that "it is likely that the major improvements in risk assessment that will be achieved in the near future will be due to improvements in our ability to estimate the uptake the chemicals caused by specific exposure scenarios.

Exposure assessments vary widely because of the kinds of information that maybe available or that are possible to obtain. The most accurate information about exposure is based on monitoring, or actual measurement, of the amounts of a substance to which people are exposed (NRC, 1991 b).

Often, however, monitoring data are not available. As a result, assessors often estimate exposures to emissions from a distant source like a factory by using exposure models (NRC, 1991 b). Exposure models simulate the dispersion of substances in the environment. Many of the hundreds of published models are quite specific for classes of substances or for the types of environments the substances travel through, such as the atmosphere, ground or surface water, or the food chain. Other models are multimedia in nature and assess the combined impact of many routes of exposure.

Exposure assessments may also account for the movement and activities of people. Over the course of a day, people spend time in their homes, their cars, and their workplaces. Their activities, as well as their locations, can have an effect on

their exposure to different substances. Exercise or work, for example, affects the rate of breathing and increases the amount of airborne substances that people inhale. Assessors can combine information on activity patterns with information on environmental concentrations to estimate exposure (Lioy, 1990; NRC, 1991a).

Risk Characterization

This final step in a risk assessment summarizes and combines the main points in the hazard identification and the dose-response and exposure assessments to provide an integrated picture of the data. It describes the conclusions reached concerning the kinds of hazards associated with exposure, whether particular subpopulations are at special risk, the assumptions that were made in arriving at the conclusions, the strengths and weaknesses of the data, and the uncertainty surrounding the conclusions. Finally, it may provide a quantitative estimate of risk or a range of possible values.

Historically, risk characterization has received much less attention than the other components of risk assessment, but that state of neglect appears to be changing (Habicht, 1992). Gray (1993) discusses recent developments in this area.

Risk characterization for noncancer effects evaluate risks against an estimated threshold level of toxicity. The Environmental Protection Agency (EPA) calls the exposure level at which risk becomes a problem the reference dose (RfD), or the acceptable daily intake (ADI). However this level is identified, it is a ballpark value. If human exposure is consistently below the RfD, risk assessors assume that there is little or no health risk. If exposures exceed the RfD significantly, they assume that a risk exists.

To determine the RfD, assessors divide the NOEL or NOAEL (determined in the dose-response evaluation) by a series of uncertainty factors or safety factors, which attempt to account for areas of uncertainty or gaps in the data (Dourson and Stara, 1983), For example, if the NOEL or NOAEL is based on data from studies in animals, it may be divided by a factor of 10 to account for the possibility that humans may be more sensitive to the chemical than the test animals. Another uncertainty factor of 10 accounts for differences in susceptibility in human populations. Usually, a NOAEL for animal studies is divided by 100 (10X 10) to develop an RfD (or ADI). When assessors are faced with the problem of developing a long-term RfD but only short-term test data are available, they may divide the NOEL or NOAEL by yet another uncertainty factor. In addition, a factor is sometimes used to account for an incomplete database. The magnitude of the uncertainty factor may vary from chemical to chemical.

When a NOEL or NOAEL is not available, assessors may use the lowest-observed-effect level (LOEL) or the lowest-observed-adverse-effect level (LOAEL) in deriving an RfD. When the LOEL or LOAEL is used, it maybe divided by an additional uncertainty factor of 10.

A variation on the uncertainty factor approach is the margin of safety (MOS), which divides the NOEL or NOAEL by the current, desired, or most feasible level of human exposure. To judge the adequacy of the MOS, it may be compared with criteria of tolerable or acceptable safety margins, which vary according to the setting (e.g., environmental or occupational) (Tardiff and Rodricks, 1987). Risk assessors generally use this approach to make judgments about the safety of existing or proposed levels of exposure.

Risk characterization differs for carcinogens. Although the extrapolation model assessors actually use may involve a number of subtle factors, all models incorporate the idea that risk varies with exposure. Therefore, by knowing the relationship between dose and risk as well as exposure, as determined in the earlier steps of the risk assessment process, it is possible to estimate the number of people who may be expected to develop cancer as a result of exposure to a chemical. But those estimates should not be considered predictions of the future incidence of

disease. The many uncertainties in each part of the assessment, the difficulties of extrapolating from the results of scientific studies to predictions of human exposure at environmental levels, and the fact that the dose-response extrapolation models are used to generate an upper bound on risk preclude precise predictions. More appropriately, these figures should be considered estimates of risk with varying ranges of uncertainty.

As other areas of risk assessment mature, signs of interest in and dissatisfaction with the current process of risk characterization are becoming apparent. Most criticism is aimed at the generation of a single numerical risk estimate that does not provide information on how it was generated or the information used in that task. Recent reports and agency communications have called on risk assessors to ''convey what is known and what is not known about a particular risk in away that accurately reflects the current state of scientific knowledge and is useful to decision makers' (AIHC, 1989); they have also defined key aspects of good risk characterization (AIHC, 1989, 1991). Former EPA Deputy Administrator F. Henry Habicht released a memo that provided guidance for agency risk assessors and risk managers on risk characterization (Habicht, 1992). The Habicht memo emphasizes that risk managers must be made aware of the strengths and limitations of a risk assessment to allow them to make "informed evaluation and use of [it]."

Several common themes are present in the reports and in the Habicht memo. Specifically, they all stress that risk characterization must characterize more completely all uncertainties, assumptions, analytical alternatives, and the full range of plausible risk estimates.

ISSUES IN HEALTH RISK ASSESSMENT

Health risk assessment has several strengths: it provides a structure for collecting, organizing, and evaluating data; it gives agencies the capacity to base decisions on estimates of risk to people; and it provides information for ranking hazards, enabling agencies to focus their resources on the most significant risks to health (U.S. EPA, 1987, 1990b). This last point has become increasingly important because the ubiquity of carcinogens and other toxic substances in the environment make it impossible to prevent all human exposure (Ames and Gold, 1990; Loehr, 1991). Aspects of health risk assessment have prompted heated debate in recent years among scientists, regulators, the regulated community, and interested citizens. The issues being debated are more numerous than can possibly be introduced here. The National Research Council, in its groundbreaking 1983 report ***Risk Assessment in the Federal Government: Managing the Process,*** identified 50 points in the risk assessment process at which scientific uncertainty is encountered and inferential bridges are needed in order to continue (box 2-B). A consensus has developed on some of these issues since the council's report was published. For example, Federal agencies have proposed using a common scaling factor for interspecies extrapolation (U.S. EPA, 1992a). Most of the issues, however, are still being discussed a decade after they were frost listed.

The section that follows describes some of the issues that arise frequently in discussions of the use of health risk assessment by Federal agencies. Further research will clarify questions that stem from missing or ambiguous data or gaps in scientific theory. (For past examples, see ch. 5.) Other issues arise, however, not because of a lack of scientific consensus but because people hold different views about how much risk is acceptable and when it is appropriate to err on the side of caution. Further research may help to refine those policy debates, but it cannot and will not end them.

Conservative Assumptions

Agencies typically deal with the kinds of issues identified by the National Research Council by choosing a standard, or default, assumption and using it consistently. In the absence of data to the

contrary, agencies have tended to choose defaults that are said to be conservative; that is, they have erred on the side of caution.

During the Bush Administration, economists from the Office of Management and Budget (OMB) as well as others (Gori and Flamm, 1991, for instance) criticized Federal regulatory agencies for using default assumptions that were, in their opinion, overly cautious and unnecessarily expensive. OMB pointed to such common practices as the use of test data from the most sensitive animal species, the choice of an extrapolation model (the linearized, multistage model) that tended to yield the highest estimates of risk, and the use of exposure models that assumed that people lived close to hazardous waste sites or other sources of exposure continuously for 70 years (Belzer, 1991; U.S. OMB, 1990-1991). According to those arguments, risks are being overestimated, leading to burdensome, unnecessary regulatory costs and a disordering of agency priorities (Barnard, 1986, 1991; Belzer, 1991; Gori and Flamm, 1991; U.S. OMB, 1990-1991),

Regulatory agencies and many analysts defend those choices as being within their mission of protecting human health, and they point out why, despite the conservatism, risks may yet be underestimated (Finkel, 1989; Huff et al., 1991; Perera and Boffetta, 1988; Rail, 1991; Silbergeld, 1993). For example, test animals are not exposed at the beginning of their lives, during fetal development, when they are more susceptible to certain agents. In addition, agencies do not consider the cumulative effect of exposure to agents from all possible routes.

Animal Bioassays

Currently, tests in rats and mice are the main tool for assessing chemicals for carcinogenicity. In the absence of data from humans, information on animals is clearly the next best basis for decisionmaking. Its supporters defend the use of the rodent bioassay as science's most important method for identifying potential human carcinogens (Cogliano et al., 1991; Huff and Rail, 1992; Perera and Boffetta, 1988; Silbergeld, 1993). Huff (1993) examined the results from 2-year carcinogenesis experiments, in both sexes of at least two animal species, on 450 chemicals and concluded that ''carcinogenicity findings from experiments in laboratory animals are scientifically reasonable for identifying and predicting potential carcinogenic effects to humans. " Indeed, all known human carcinogens have been found to be carcinogenic in at least one other animal, although that fact does not necessarily mean that the converse is true, that is, that all animal carcinogens are carcinogenic in humans (U.S. OSTP, 1985).

Critics, however, have pointed out a number of problems with current testing methods. The traditional long-term carcinogen bioassay is quite expensive and time-consuming, so the number of animals it uses must be limited. To increase the likelihood of identifying carcinogens, researchers administer high doses of the test chemical. The highest dose used, the maximum tolerated dose (MTD), is that quantity of the substance that is just large enough to elicit signs of minimal toxicity without significantly altering the animal's lifespan as a result of effects other than carcinogenicity (NRC, 1993; U.S. OSTP, 1985). Lower doses, such as one-half the MTD, are also given. Unlike test animals, humans are rarely exposed to such high levels, aside from accidents and some workplace exposures, and never over their entire lifespan. Researchers assume, however, that if a chemical causes an increase in the incidence of cancer at a high dose, it will also cause cancer, albeit at lower frequencies at lower doses.

For agents like ionizing radiation and some chemicals, substantial scientific evidence supports that assumption (Huff et al., 1991). But others argue that at such high doses, many chemicals tested are carcinogenic (Ames and Gold, 1990), They suggest that this result may be due to secondary effects that do not occur at lower doses. They further suggest that doses at the MTD

Box 2-B-issues in Health Risk Assessment

HAZARD IDENTIFICATION

Epidemiologic Data

- What relative weights should be given to studies with differing results? For example, should positive results outweigh negative results if the studies that yield them are comparable? Should a study be weighted in accord with its statistical power?
- What relative weights should be given to results of different types of epidemiologic studies? For example, should the findings of a prospective study supersede those of a case-control study, or those of a case-control study those of an ecologic study?
- What statistical significance should be required for results to be considered positive?
- Does a study have special characteristics (such as the questionable appropriateness of the control group) that lead one to question the validity of its results?
- What is the significance of a positive findingin a study in which the route of exposure is different from that of a population at potential risk?
- Should evidence on different types of responses be weighted or combined (e.g., data on different tumor sites and data on benign versus malignant tumors)?

Animal-Bioassay Data

- What degree of confirmation of positive results should be necessary? Isa positive result from a single animal study sufficient or should positive results from two or more animal studies be required? Should negative results be disregarded or given less weight?
- Should a study be weighted according to its quality and statistical power?
- How should evidence of different metabolic pathways or vastlydifferent metabolic rates between animals and humans be factored into a risk assessment?
- How should the occurrence of rare tumors be treated? Should the appearance of rare tumors in a treated group be considered evidence of carcinogenicity even if the finding is not statistically significant?
- How should experimental-animal data be used when the exposure routes in experimental animals and humans are different?
- Should a dose-related increase in tumors be discounted when the tumors in question have high or extremely variable spontaneous rates?
- What statistical significance should be required for results to be considered positive?
- Does an experiment have special characteristics (e.g., the presence of carcinogenic contaminants in the test substance) that lead one to question the validity of its results?
- How should findings of tissue damage or other toxic effects be used in the interpretation of tumor data? Should evidence that tumors may have resulted from these effects be taken to mean that they would not be expected to occur at lower doses?
- Should benign and malignant lesions be counted equally?
- Into what categories should tumors be grouped for statistical purposes?
- Should only increases in the numbers of tumors be considered, or should a decrease in the latent period for tumor occurrence also be used as evidence of carcinogenicity?

Short-Term Test Data

- How much weight should be placed on the results of various short-term tests?
- What degree of confidence do short-term tests add to the results of animal bioassays in the evaluation of carcinogenic risks for humans?
- Should in vitro transformation tests be accorded more weight than bacterial mutagenicity tests in seeking evidence of a possible carcinogenic effect?

- What statistical significance should be required for results to be considered positive?
- How should different results of comparable tests be weighted? Should positive results be accorded greater weight than negative results?

Structural Similarity to Known Carcinogens

. What additional weight does structural similarity add to the results of animal bioassays in the evaluation of carcinogenic risks for humans?

General

- What is the overall weight of the evidence of carcinogenicity? (This determination must include a judgment of the ***quality of*** the data presented in the preceding sections.)

DOSE-RESPONSE ASSESSMENT'

Epidemiologic Data

- What dose-response models should be used to extrapolate from observed doses to relevant doses?
- Should dose-response relations be extrapolated according to best estimates or according to upper confidence limits?
- How should risk estimates be adjusted to account for a comparatively short followup period in an epidemiologic study?
- For what range of health effects should responses be tabulated? For example, should risk estimates be made only for specific types of cancer that are unequivocality related to exposure, or should they apply to all types of cancer?
- t-low should exposures to other caranogens, such as cigarette smoke, be taken into consideration?
- How should one deal with different temporal exposure patterns in the study population and in the population for which risk estimates are required? For example, should one assume that lifetime risk is only a function of total dose, irrespective of whether the dose was received in early childhood or in old age? Should recent doses be weighted less than earlier doses?
- How should physiologic characteristics be factored into the dose-response relation? For example, is there something about the study group that distinguishes its response from that of the general population?

Animal-Bioassay Data

- What mathematical models should be used to extrapolate from experimental doses to human exposures?
- Should dose-response relations be extrapolated according to best estimates or according to upper confidence limits? If the latter, what confidence limits should be used?
- What factor should be used for interspecies conversion of dose from animals to humans?
- How should information on comparative metabolic processes and rates in experimental animals and humans be used?
- If data are available on more than one nonhuman species or genetic strain, how should they be used? Should only data on the most sensitive species or strain be used to derive a dose-response function, or should the data be combined? If data on different species and strains are to be combined, how should this be accomplished?
- How should data on different types of tumors in a single study be combined? Should the assessment be based on the tumor type that was affected the most@ some sense) by the exposure? Should data on all tumor types that exhibit a statistically significant dose-related increase be used? If so, how? What interpretation should be given to statistically significant decreases in tumor incidence at specific Sites?

(continued *on next page)*

Box 2-B-issues in Health Risk Assessment-Continued

EXPOSURE ASSESSMENT

- How should one extrapolate exposure measurements from a small segment of a population to the entire population?
- How should one predict dispersion of air pollution into the atmosphere due to convection, wind currents, etc., or predict seepage rates of toxic chemicals into soils and groundwater?
- How should dieter habits and other variations in lifestyle, hobbies, and other human activity patterns be taken into account?
- Should point estimates or a distribution be used?
- How should differences in timing, duration, and age at first exposure be estimated?
- What is the proper unit of dose?
- How should one estimate the size and nature of the populations likely to be exposed?
- How should exposures of special risk groups, such as pregnant women and young children, be estimated?

Risk Characterization

- What are the statistical uncertainties in estimating the extent of health effects? How are these uncertainties to be computed and presented?
- What are the biologic uncertainties in estimating the extent of health effects? What is their origin? How will they be estimated? What effect do they have on quantitative estimates? How wil the uncertainties be described to agency decisionmakers?
- Which population groups should be the primary targets for protection, and which provide the most meaningful expression of the health risk?

[1] Current methods and approaches to exposure assessment appear to be medium- orroute-specific. In contrast with hazard identification and dose-response assessment, exposure assessment has very few components that could be applicable to all media.

SOURCE: National Research Council, *Risk Assessment in the Federal Government:* Managing the Process (Washington, DC: National Academy Press, 19S3).

may cause chronic cell killing and consequent increased cell division, which in turn causes increased rates of mutagenesis and carcinogenesis (Ames and Gold, 1990; Cohen and Ellwein, 1990, 1991a, 1992).

The use of the MTD was the focus of a recent report by the National Academy of Sciences. In an unusual occurrence for an academy committee, the participants failed to reach a consensus. Two-thirds of the 17-member panel favored continuing the use of the MTD, and one-third favored the use of more moderate doses (NRC, 1993; ***Science, 1993).*** Clearly, this issue remains unresolved.

Some carcinogenic mechanisms and pathways that occur in animals may not occur in humans. For example, unleaded gasoline, d-limonene, and 1,4-dichlorobenzene cause kidney tumors in male rats but not in mice or female rats. These substances appear to induce accumulation of a protein found only in adult male rats, which appears to be responsible for increased cell death and concomitant cell regeneration (U.S. EPA, 1991a). Because that protein does not occur in humans, substances that cause tumors in the kidneys of male rats through this mechanism may not be human carcinogens. Better understanding of the basic mechanisms of chemical carcinogenesis should help to resolve these and similar issues.

Models for Dose Extrapolation

Research has developed a number of different statistical "models for extrapolating from high to low doses, and all of them generally fit the data in the range of doses used in animal tests. (The White House Office of Science and Technology Policy offers a good description of various models; see U.S. OSTP, 1985.) However, the models can differ significantly in the low-dose region, the area of primary interest to risk assessment (Paustenbach, 1989a). In general, the one-hit model and the linearized, multistage model (LMS,) predict the highest risk (Munro and Krewski, 1981). EPA prefers the LMS model "in the absence of adequate information to the contrary' (U.S. EPA, 1986a).

All of the models now in use are based on the current scientific understanding of carcinogenesis induced by ionizing radiation or by one particular class of chemical carcinogens known as genotoxins, which interact with DNA. There is growing evidence, however, that these models may be inappropriate for other kinds of chemical carcinogens, some of which may even have thresholds. EPA has stated that it recognizes that the LMS model should not be used for certain chemicals; however, it prefers this model for chemicals whose mechanisms of action are unknown. Some observers have suggested that a better approach might be to report results using more than one model, citing the lack of evidence that the LMS model predicts the low-dose response better than other models (Paustenbach, 1989a).

Critics have charged that current models are ''overly simplistic. probabilistic representations of highly complex biological phenomena' (Sielken, 1987). They contend that the models do not take into account current knowledge of the mechanisms of carcinogenesis or the impact of other biological processes such as rates of cell turnover, repair processes, immune system responses, and physiological and pharmacokinetic models of the absorption, delivery, metabolism, and elimination of chemicals. Such critics suggest that methods be developed to permit consideration of more biological information in quantifying the dose-response relationship (Barnard, 1991; Cohen and Ellwein, 1991b; Sielken, 1987).

Weight of the Evidence

Scientific studies vary in their quality, but regulatory agencies tend to place heavy emphasis on any study suggesting that a chemical might be hazardous, regardless of the quality of the research. Increasingly, however, agencies are responding to criticisms of this practice by adopting a weight-of-the-evidence approach (U.S. EPA, 1986a, 1992b). That approach takes into consideration the quality and adequacy of the available data and the kinds and consistency of responses induced by a suspected toxic substance (U.S. EPA, 1986a; U.S. OSTP, 1985).

Evaluating Mixtures of Chemicals

People are exposed to multiple substances simultaneously, but with few exceptions, chemicals are studied and regulated individually. Little is known about the effects of most chemicals when encountered in mixtures. In fact, many components of common mixtures may be unknown. It is usually assumed, for the purposes of risk assessment, that each substance exerts its effect independently and that the effects are simply additive. Researchers have found examples, however, of substances whose toxic effects are not additive. For example, exposure to either tobacco smoke or radon is associated with an increased risk of lung cancer. Exposure to both poses an even greater risk than would be predicted by an additive model (see ch. 6). Such an effect is said to be synergistic. Although fewer cases are known, examples also exist of substances that show antagonistic effects; that is, when the substances are administered together, the toxic effects are less than the sum of the effects when each is administered individually. For example, administering dioxin before administering another carcin-

ogen reduces the rate of cancer. For most chemicals, however, such data are unavailable.

Chemical mixtures may be regulated as such (e.g., coke oven emissions or diesel exhaust) if data on the mixture itself are available. If they are not, assessments may be based on the data collected about a similar mixture or on some of the components of the mixture. EPA's guidelines for the health risk assessment of chemical mixtures (U.S. EPA, 1986b) recommend that assessors assume that effects are additive, that interactions decrease significantly with decreasing doses, and that they seldom play a role at the usual, low levels of human exposure.

Characterizing Uncertainties and Assumptions

Acceptance is growing for the need to move beyond simple numerical estimates of risk and to give risk managers a broader picture of the uncertainties associated with risk estimates (Habicht, 1992). When health risk assessments discuss uncertainties, they tend to take the form of lists of uncertain assumptions. It is unclear whether that practice improves the decisionmaking process. Some analysts have proposed a more complete picture of risk by replacing point estimates with uncertainty distributions that would show all the possible values of the risk and their associated probabilities of occurrence (Finkel, 1990).

Few in the risk assessment field would argue with the notion that the estimates provided by risk assessment are highly uncertain. In hazard identification, the exact relationship of animal tests to human risk and the predictive value of high-exposure occupational epidemiology to environmental exposures are quite unclear. There is generally no way to determine the most appropriate mathematical model for extrapolating from high to low doses in dose-response evaluation. And methods of exposure assessment, especially when exposure may be from many pathways, are rudimentary. All of these factors contribute to the great uncertainty present in estimates of risk (Rosenthal et al., 1992).

According to Gray (1993) and others (AIHC, 1989, 1991), making that uncertainty known to all of the users of a risk assessment is of paramount importance. As Habicht (1992) states, ' 'uncertainty should be acknowledged and expressed both qualitatively and quantitatively.' His memo directed EPA personnel to develop a statement of confidence in a given risk assessment and emphasized that identifying uncertainties is a key component of such a statement. In addition, Habicht emphasized that numerical risk estimates must not be allowed to stand alone, separated from the various assumptions and uncertainties on which they are based.

Current and future scientific research will help reduce the uncertainties in many aspects of risk assessment. Today, however, in the absence of definitive science, a number of default assumptions are made. For example, current practices in hazard identification assume that any animal carcinogen has the potential to be a human carcinogen even though exceptions to this rule are thought to exist; current dose-response evaluation assumes that the dose-response function for carcinogens has no threshold; and exposure assessments assume that maximally exposed individuals spend their entire 70-year lifetime at the point of maximum exposure. Some of the assumptions used in risk assessment are generally accepted, but others are matters of contention. Furthermore, a distinction can be made between science-based issues that can be answered experimentally and policy issues that are based on values and cannot be addressed by research.

WHY CONDUCT RISK ASSESSMENT RESEARCH?

Risk assessment—through its incorporation into dozens of Federal, State, and local laws and regulations—influences the expenditure of hundreds of billions of dollars in the domain of health and environmental protection. Accurate risk as-

sessment demands extensive knowledge that only research can generate. The approaches used in risk assessment depend on research findings. It is typically the lack of data and knowledge that limits the accuracy of, and confidence in, a given assessment.

Policymakers depend on health risk assessment and research in making regulatory decisions about which risks to tolerate and which to reduce or prevent. They also have to weigh the costs and benefits associated with those decisions. Overly cautious decisions to reduce the risks posed by contaminants in the environment, for example, may mean inappropriate expenditures of limited national resources for environmental cleanup operations. Complacent decisions to tolerate risks may result in increases in environmentally related illness.

The costs of complying with environmental regulations and the costs of environmentally related illnesses are discussed here as an illustration. The purpose of this discussion is not to argue the merits or costs and benefits of individual regulatory decisions but rather to capture the general magnitude of the public health, environmental, and economic interests at stake.

Hahn and Hird (1991) determined that the annual costs of environmental regulation alone in 1988 were between $55 and $135 billion, and the benefits were between $16 and $135 billion. These estimates do not include the costs and benefits of regulations covering the occupational workplace, consumer product, and food safety, Senator Daniel P. Moynihan's "Environmental Risk Reduction Act of 1993" (S. 110) states that the annual cost of protecting the Nation's environment is more than $115 billion. Moynihan said on introducing the bill that although ''this may not be too much money to spend on environmental protection, it is too much to spend unwisely. With so much riding on regulatory decisions, the Office of Technology Assessment (OTA) concludes that the time is ripe for attention to the foundation of those choices: research and its contribution to risk assessment.

The Costs of Compliance

What level, if any, of exposure to a chemical is ''safe' or tolerable? How clean must a waste site be to be considered cleaned up? Risk assessment cannot answer those questions because concepts of equity as well as laws and regulations play a role. It can, however, provide estimates of the harm that may result from inaction or from various actions. Those estimates can guide and inform regulators, influencing how billions of dollars may be spent on regulatory decisions to reduce cur-rent or prevent future exposure to potentially hazardous chemicals. That type of cost, which is incurred by complying with a law or regulation, is generally referred to as a compliance cost. The costs of handling, treating, and disposing of solid and hazardous wastes are examples of compliance costs.

In fiscal 1993, Congress appropriated more than $9 billion for environmental cleanup at Federal facilities of the Departments of Energy and Defense, an amount much larger than the $1.6 billion appropriated for cleaning abandoned hazardous waste sites under the Superfund legislation. (That effort is financed partly by a tax on the chemical industry and partly from general revenues.) As a direct result of such cleanup activities focused on military and nuclear waste, EPA has projected that Federal cleanup expenditures will increase by 140 percent over the 1987-2000 period (U.S. EPA, 1990a). In other words, the costs of compliance increasingly fall directly on the Federal Government.

The cost of complying with EPA regulations is not the only type of compliance cost, but it is the best documented. Compliance with Food and Drug Administration (FDA) regulations also consumes substantial resources, but a formal estimate is not available, The Pharmaceutical Manufacturers Association, however, states that its members spent $9.2 billion for research and development in 1991, some portion of which represented toxicity and safety testing to satisfy FDA regulatory requirements (PMA, 1991). Sim-

ilarly, compliance costs are incurred by complying with the rules and regulations promulgated by the Occupational Safety and Health Administration and the Consumer Product Safety Commission.

Costs of Environmentally Related Illnesses

Besides compliance costs, there are other risk-related costs. For example, what are the costs of existing environmentally related illnesses, and how would future costs be affected by regulatory decisions?[2]

The answers to those questions can only be estimated. Estimating the costs of some environmentally related illnesses is easier than assessing how regulatory decisions are likely to affect their costs. Regulatory decisions have a bearing on the costs of environmentally related illnesses, but the relationship is not as straightforward as that between regulation and the cost of compliance.

The costs of some environmentally related illnesses have been estimated to reach well into the billions of dollars, although no comprehensive estimates are available. The Institute of Medicine, for example, attempted to quantify such costs in 1981 in response to a congressional mandate (P.L. 95-623). The institute determined, however, that it was not possible at that time to document the costs of environmental pollution (the main focus of the study). Instead, it offered an extensive plan of study that would fulfill the goal envisioned by Congress (IOM, 1981).

Studies that attempt to assess the economic burden of illnesses generally rely on epidemiologic estimates of the number of people afflicted (i.e., the prevalence of disease), national surveys of health care expenditures, and studies that assign monetary values to disability and premature death. Because cost-of-illness studies are difficult to perform and depend heavily on the definitions of direct and indirect medical costs that researchers use, those who employ and interpret them must exercise caution. Direct costs usually include inpatient and outpatient expenditures; indirect costs may include costs related to loss of work, years of productive life lost, quality of life, and premature death.

One example of the costs associated with environmentally related illnesses comes from lead poisoning, a preventable environmental hazard that may affect the cognition, behavior, endocrinology, and growth of children in the United States (U.S. DHHS, 1991a). It is estimated that 250,000 children have lead levels greater than 25 micrograms per deciliter (ug/dl) of blood and require medical treatment and special education averaging about $4,600 per child (U.S. DHHS, 1991 b).

Although EPA has not performed a comprehensive study of the costs of lead exposure from all sources, it has analyzed the costs associated with exposure to some sources of lead. For drinking water, EPA's Regulatory Impact Analysis assigned a range of monetary values to the projected health benefits for children and adults of reducing exposure to lead from that source. The direct and indirect medical benefits (quantified as savings) that are expected to occur annually when States eventually meet EPA's new drinking water standards were estimated at between $2.8 and $4.3 billion (U.S. EPA, 1991 b). (The estimate is based on lead's adverse effects on adult male blood pressure and children's intelligence.)

It should be noted that overall mean blood lead levels declined by 37 percent during the 1976-80 period (Farfel, 1985), when lead in gasoline was reduced as a result of the passage of the Clean Air Act. In 1985, EPA estimated that its further phase-downs of the lead content of gasoline ordered in that year would produce health benefits for children and adults valued at approximately

[2]This question addresses the current economic burden of environmentally related illness. It might also be posed as, what are the savings or benefits of preventing environmentally related illnesses? It is a matter of convention regarding whether to cast the question in terms of costs or benefits, because economists typically define costs and benefits in opposition to one another.

$5 billion in 1992, based on 1983 dollars (U.S. EPA, 1985).

Analysts can also estimate the health costs that arise from other environmentally related diseases, which cannot be sufficiently discussed here. Relevant examples include respiratory problems from air pollution and environmental tobacco smoke, and occupational diseases such as mesothelioma from exposure to asbestos.

The Role of Research

Controversies or conservative assumptions in risk assessment stem from the lack of data or scientific knowledge about the risks being assessed. With so much at stake, it seems fitting to seize the opportunity of using scientific research to narrow the scope of uncertainty in health risk assessment.

In 1983, the National Research Council (NRC) concluded that improving the quality and comprehensiveness of the knowledge used in risk assessment is by far the most effective way to improve the process (NRC, 1983). The decade following publication of the NRC report saw impressive advances in the biological and biomedical sciences. Is an appropriate investment being made in research to harness those advances in developing a better knowledge base for health risk assessment?

In this report, OTA analyzes the resources devoted to such development. It also examines the nature, organization, and management of federally supported research on health risk assessment and whether this area of research is adequately supported. Subsequent chapters discuss how priorities are set for health risk assessment research and the relationship of this area of research to regulatory decisionmaking.

SUMMARY

Health risk assessment offers a systematic approach to evaluating data and formulating judgments about risk. It consists of some or all of the following four steps: hazard identification, dose-response analysis, exposure assessment, and risk characterization.

The primary source of data for assessing risks to human health is epidemiologic, toxicological, structure-activity relationship, and exposure studies. However, the data such studies provide are usually incomplete for evaluating the risk from the exposures being considered. Researchers therefore use various extrapolations (e.g., from high to low doses, animals to humans, and ingestion to inhalation) to predict the possible outcomes from the available data.

To perform those extrapolations, Federal agencies use assumptions or policy positions to bridge gaps in the data or knowledge. Because assumptions and policy positions contain value judgments and a large measure of scientific uncertainty, they are the main areas of controversy in risk assessment.

However uncertain the results of health risk assessment may be, they provide the scientific foundation for decisions about how to mitigate health risks (e.g., emission standards for incinerators). Those decisions, and the standards that are their frequent consequence, can lead to expenditures for compliance with regulations and medical expenses for exposure-related diseases that may run into billions of dollars.

With so much at stake and given the opportunity presented by advances in the biological and biomedical sciences, research is capable of narrowing the uncertainties in health risk assessment. This report reviews the Federal Government's research efforts to determine whether appropriate attention is being given to this field.

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