Chapter 6

Assessing and Managing Risk

'The alternative to not performing risk assessment is to adopt a policy of either reducing all *potentially toxic* emissions to the greatest degree technology allows or banning all substances for which there is any evidence of harmful effect, a policy that no technological society could long survive. "

William D. Ruckelshaus
Issues in Science and Technology
Spring 1985

"Risk assessment has become a central focus of environmental policy in the past couple years. In part, this is a matter of fashion. But it also arises from the real need to compare the relative importance of the vast number of environmental threats, because it has become obvious that not all threats can receive maximum attention.'

William K. Reilly
The Conservation Foundation
1985

"Over the past decade increasingly sophisticated methods have been developed to identify health hazards and assess risks quantitatively. But society has yet to agree on the most critical step in risk management: identifying risk goals and translating them into practical regulations. Does society seek to eliminate all risks, eliminate all nontrivial risks, all significant risks, or only those risks that are not outweighed by benefits?"

Daniel Byrd and Lester B. Lave
Issues *in Science and Technology*
Summer 1987

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Risk assessment is the analytical process by which the nature and magnitude of risks are identified. Risk, as it pertains to the health effects of toxic substances, is the probability of injury, disease, or death for individuals or populations undertaking certain activities or exposed to hazardous substances. It is sometimes expressed numerically (e.g., 1 in 1 million); however, quantification is not always possible, and risk may sometimes be expressed in qualitative terms such as high, medium, or low risk.

Risk management, a process guided by risk assessment, and by political, social, ethical, economic, and technological factors as well, involves developing and evaluating possible regulatory actions and choosing among them (15). The four components of risk assessment and the process of risk management are summarized in figure 6-1 and are discussed in more detail below. In practice, risk assessment and risk management frequently overlap and become difficult to distinguish (27). This is partly because definitions such as "adverse,' "harmful," and "toxic" involve both scientific and social judgments.

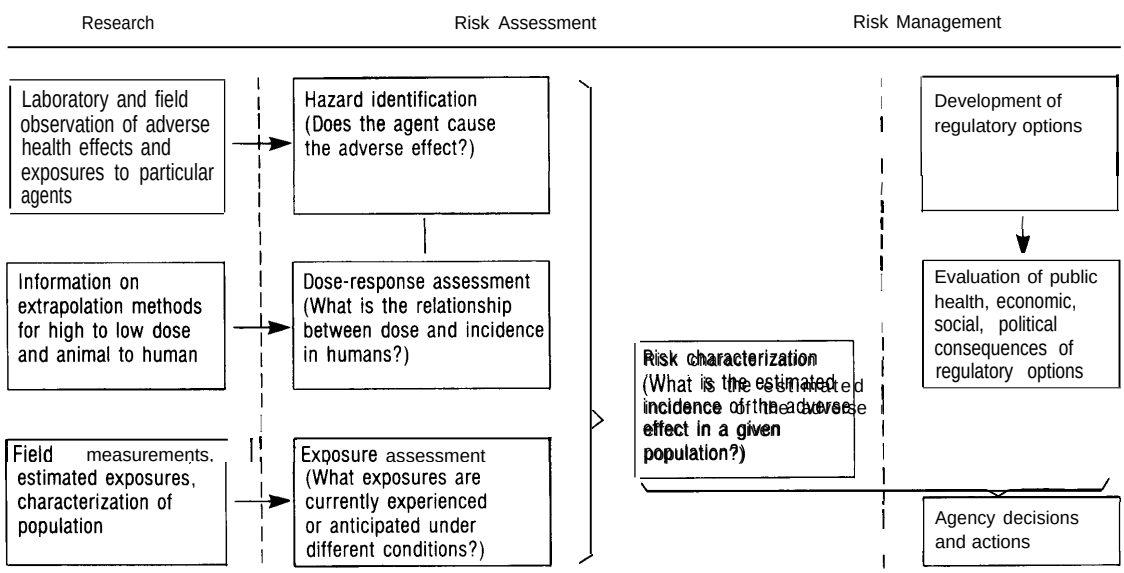
Some degree of risk is associated with almost every aspect of modern living. For example, traveling in an automobile involves a risk of accidental death of 1 in 4,000, a relatively high risk. In contrast, the risk of being killed by lightning is 1 in 2 million. Whether a risk is acceptable or not depends on many factors, including benefits. Defining acceptable risk is the task not only of scientists and regulatory officials, but of society in general. Everyone evaluates risks on a daily basis and makes individual choices depending on experience and numerous other factors. At times, one's perception of risk may not be entirely logical. For example, some people are reluctant to travel by air, even though the risk of death associated with automobile travel is 25 times greater (table 6-1) (13). People tend to overestimate the number of deaths from rare, dramatic risks and

Table 6-l-Estimated Risk of Death to an individual 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 2.000.000

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

Figure 6-l-The Relationship Between Risk Assessment and Risk Management

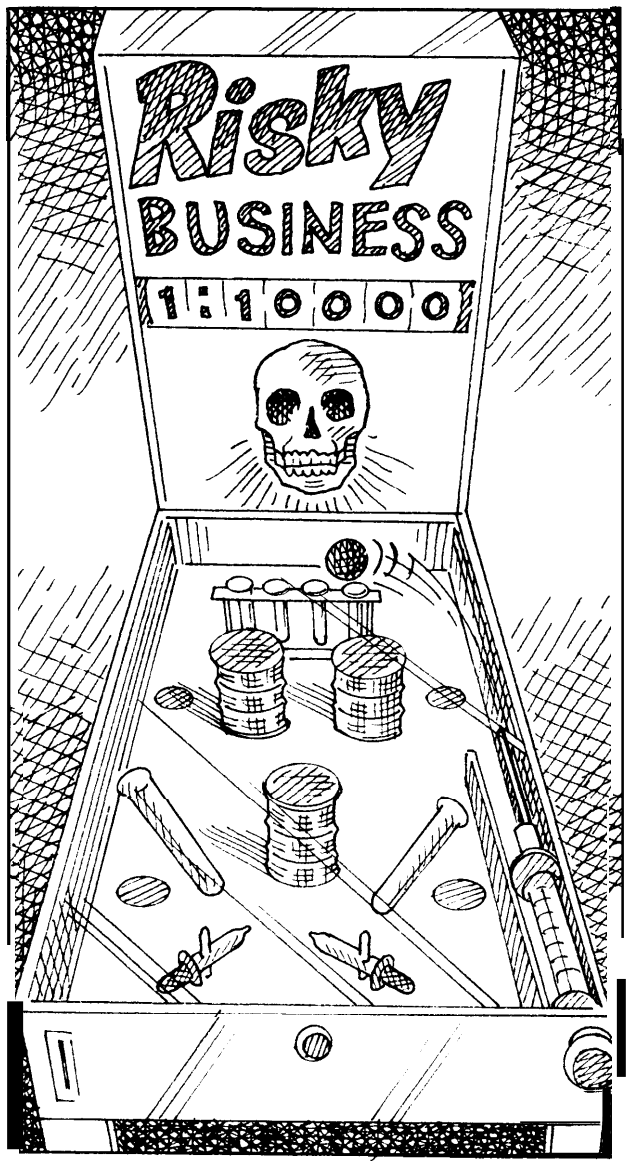


SOURCE: National Research Council, *Risk Assessment in the Federal Government: Managing the Process* (Washington, DC: National Academy Press, 1983).

underestimate the number from common, undramatic causes (6). For example, public perception of the annual death rates from floods or tornadoes are typically overestimated, while the risk from smoking or drinking alcoholic beverages is typically underestimated (6).

Risk assessment practices are the subject of ongoing debate within the regulatory and scientific communities, and in the last two decades strategies for regulating toxic substances have changed considerably. In the early 1970s, environmental legislation focused on regulating a relatively small number of pollutants of known toxicity. Today, concern is focused on thousands of toxic substances, for many of which little information is available. Consequently, regulatory strategies have changed. This change has been forced in part by improved methods of detecting toxic substances in the environment, improved capability of identifying the adverse effects of those substances, and difficulty in determining threshold levels below which no adverse effects occur. A major question facing both regulators and the public is how much risk is acceptable. A wide variety of views has been expressed on the topic of acceptable risk (4,6). A risk of death of less than 1 in 100,000 (10^{-5}) to 1 in 1 million (10^{-6}) is sometimes considered an acceptable risk for exposure to a chemical (13).

Policies regarding risk assessment have been controversial. Some people believe that Federal agencies overestimate risk by making overly conservative assumptions in developing risk assessments. Others feel that risk assessment practices do not take into account the complex interactions of multiple pollutants that often occur in the environment. Still others point out that risk assessments focus primarily on adverse effects on human health and devote little attention to other organisms and the environment in general. Critics of established risk assessment procedures believe that too little attention is being paid to the potential effects of toxic substances on children, infants, and the unborn, and efforts to address these concerns are under way at regulatory agencies. Regardless of the various viewpoints, risk assessment has become an integral component of regulatory strategies, and it is important to appreciate the scientific issues underlying this process in order to understand how toxic substances are controlled (6).



illustrated by: Ray Driver

In this chapter, the basic principles of risk assessment as they relate to the neurotoxicity of industrial chemicals are described. The risks posed by pharmaceuticals, for example, are typically evaluated through other approaches. The Environmental Protection Agency (EPA) has actively pursued regulatory strategies based on risk assessment (17), and the National Research Council (NRC) of the National Academy of Sciences has examined the issue of evaluating the risk posed by neurotoxic

substances. The reader may wish to refer to the NRC report for further information on this subject (16).

RISK ASSESSMENT

A complete risk assessment comprises four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization (15). Each of these is discussed in the sections that follow.

Hazard Identification

Hazard identification involves gathering and evaluating toxicity data on the types of injury or disease that may be produced by a substance and on the conditions of exposure under which the injury or disease may be produced. Toxicity data typically derive from epidemiological and experimental animal studies. Hazard identification involves judgments about the quality and relevance of these data. Of special importance is the question of whether specific toxic effects observed in one human population or in a particular experimental setting are likely to be produced in populations for which such data have not been or cannot be collected.

The most relevant toxicity data for identifying human hazards are usually derived from studies in humans. However, such information is often unavailable or limited and can be obtained only *after* human exposure has occurred. Consequently, it has become common practice to rely on data from animal studies to assess the toxic properties of chemicals. As discussed in chapter 5, a substantial body of evidence indicates that results from animal studies, with appropriate adjustments and qualifications, can be used to infer human hazard (1 3). There are important exceptions to this generalization, but unless existing data on human toxicity convincingly contradict a specific finding in animals, or there are other physiological reasons to consider certain types of animal data irrelevant to humans, the assumption is generally made that animal toxicity data can be used to identify potential human hazards (8).

The hazard identification section of a risk assessment report typically includes an evaluation of all available toxicity data to identify those adverse effects that are best documented and those that are most relevant to human health. In most cases, the toxic effects **causing greatest concern are those that** are most severe, occur at lowest exposures, and persist after exposure ceases.

A complete hazard identification also includes a discussion of the limitations of the available data. The absence of relevant data cannot, of course, be taken as evidence that a particular substance does not pose a hazard.

Dose-Response Assessment

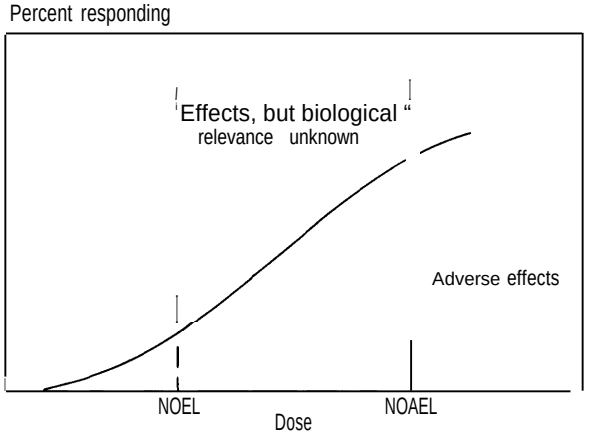
In the second step of risk assessment, assessors derive the quantitative relationship between exposure to a substance, usually expressed as a dose, and the extent of toxic injury or disease. There may be more than one relationship per substance, because several different kinds of responses may be elicited.

For any given chemical and exposure route, the severity and frequency of an effect generally increase with dose. Because humans are typically exposed at lower doses than those used in toxicity studies, it is necessary to *extrapolate* dose-response relations. At present, there are differences between dose-response extrapolations for noncarcinogenic types of toxicity, such as neurotoxicity, and for carcinogenicity. Noncarcinogenic effects are generally assumed to occur only when a certain level of exposure has been exceeded. This level is referred to as the threshold. It is frequently assumed that most carcinogens pose some risk at any level of exposure. However, the assumption that there is a threshold for all neurotoxic substances is questioned by some scientists (21).

The dose-response evaluation for noncarcinogens is derived from observations of a no observed effect level (NOEL) or no observed adverse effect level (NOAEL) in exposed people or experimental animals (figure 6-2). The NOAEL or NOEL represents an approximate threshold for the group that has been studied. The NOEL is that dose at or below which *no* biological effects of any type are noted (a determination that is influenced by the sensitivity of analytical techniques), and the NOAEL is that dose at or below which no *harmful* effects are seen. As noted earlier, definitions of "harmful" effects are influenced by social norms and values. If more than one effect is seen in animal tests, the effect occurring at the lowest dose in the most sensitive animal species and sex is generally used as the basis for estimating a NOEL or NOAEL. The NOAEL is most commonly used in current neurotoxicological evaluations.

Experimental studies are often conducted using relatively high doses of a chemical to increase the probability of observing effects in small groups of

Figure &2—Hypothetical Placement of a No Observed Effect Level (NOEL) and No Observed Adverse Effect Level (NOAEL) for a Single Chemical on a Dose-Response Curve



SOURCE: Office of Technology Assessment, 1990.

animals. Human exposures tend to be in low doses, where responses are not generally directly observable. Therefore, in moving from laboratory exposures to human exposures, it is usually necessary to extrapolate from high dose-responses to low dose-responses. Extrapolations are also necessary to adjust for differences between animals and humans with regard to conditions of exposure and certain physiological factors, such as size, lifespan, metabolism, brain maturation rate, and absorption. Adjustments are also made for variations in sensitivity among individuals in a population (intraspecies differences) (15). Some of these extrapolations and adjustments take the form of safety factors; these are discussed in more detail in the risk characterization section of this chapter.

Exposure Assessment

The next step in risk assessment is determination of the extent and nature of human exposure (including source, route, dose, and duration). An assessment of subgroups in the population expected to experience unusual exposures is also appropriate (15).

Exposure can occur from many sources (e.g., soil, food, air, or water) and may enter the body by several routes, including ingestion, inhalation, or contact with skin. It is important to note that an individual may incur exposures from more than one source or route. Determination of environmental concentrations and means of human exposure, route of entry, site of the exposed population, and uncertainties in exposure estimates are important factors in exposure assessment. The degree of exposure to some toxic substances is strongly influenced by occupation. For example, industrial workers may be exposed to high concentrations of some chemicals that the public may encounter at much lower levels.

Duration refers to the period of time over which individuals are exposed. An acute exposure is generally a single exposure that occurs over a short period of time. An exposure is considered chronic when it occurs over extended periods of time or a substantial portion of a person's lifetime (see ch. 5). Exposures of intermediate duration are called subchronic. Chronic and subchronic exposures may be episodic (occurring at various intervals) or continuous (occurring over extended periods).

The pattern of exposure-the dose, duration, frequency, and route—is an important determinant of risk. Other concerns include knowledge of the age, sex, health status, and presence or absence of other environmental exposures for a given population. Obtaining such information requires a comprehensive monitoring program; however, data of this kind for a given toxic substance are often not available.

Risk Characterization

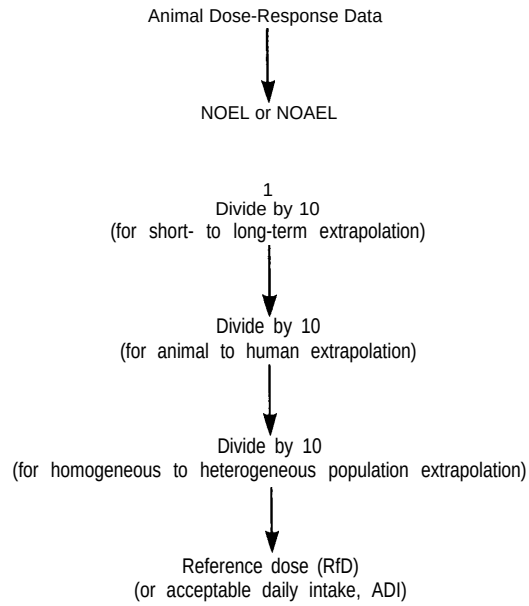
The final step of risk assessment combines the results of hazard identification, dose-response assessment, and exposure assessment to produce a characterization of risk. The NOAEL (or, less frequently, the NOEL) derived in the assessment of dose-response is divided by a safety factor, or uncertainty factor, yielding what is called the reference dose (RfD) (2). At **the present time,** risk characterization for noncarcinogenic forms of toxicity, including neurotoxicity, is based on the NOAEL (or NOEL) safety factor approach. The RfD (also called the acceptable daily intake)[1] is used to characterize risk. If human exposure is consistently below the RfD, risk assessors assume there is little health risk. If exposures exceed the RfD, it is assumed a significant risk exists. Generally, no

[1]Reference dose is considered by EPA to be a more appropriate term than acceptable daily intake, in part because of the difficulty of defining "acceptable."

attempt is made to describe the magnitude of the risk.

Three safety factors are commonly used to develop an RfD. The NOAEL or NOEL is divided by 10 when epidemiological or human experimental data are used to predict human risk. This safety factor is applied in order to protect sensitive members of the population when data have been obtained from average, healthy persons. Another factor of 10 is applied to the NOAEL or NOEL when extrapolating from animals to humans. To develop a chronic RfD when only subchronic animal studies are available, another factor of 10 is added, for a total safety factor of 1,000. Sometimes a factor is added for an incomplete database. The magnitude of the safety factor employed can vary from chemical to chemical. Scientific judgment may be exercised in evaluating species differences, the nature and extent of human exposure, the types of toxic effects, and the relative doses at which toxicity occurs in test species (see, e.g., 51 FR 34040). The application of safety factors is diagramed in figure 6-3.

Figure 6-3-Use of Safety Factors in Deriving a Reference Dose



SOURCE: Office of Technology Assessment, 1990.

A variation on the safety factor approach is the margin of safety (MOS), or margin of exposure (MOE). This involves dividing the NOAEL (or NOEL) by the current, desired, or most feasible human exposure level. This margin is sometimes compared with the safety factors mentioned above in order to judge its adequacy. Risk assessors generally employ the MOS approach to make judgments about the safety of existing or proposed exposure levels. They use the safety factor approach in circumstances where guidelines or regulations specify maximum allowable or safe exposure limits (3).

For substances that produce carcinogenic effects, the NOAEL (or NOEL) safety factor approach is not used. Instead, various extrapolation models are applied to develop estimates of risk (typically, the probability of developing cancer over a lifetime) associated with various levels of exposure. There is little scientific literature on the application of this type of extrapolation to noncarcinogenic effects.

Currently, cancer risks and RfDs are expressed numerically, but these quantitative figures may be qualified with factors such as the strength of the evidence of toxicity on which the risk or RfD is based. The uncertainties and assumptions inherent in any risk assessment should also be stated. This information is as essential as the quantitative description of risk associated with exposure to a toxic substance.

RISK MANAGEMENT

The purpose of risk management is to determine whether an assessed risk should be reduced and to identify the degree of risk reduction that is appropriate to a given situation. Risk management depends on information derived from the risk assessment, but it may also depend on political, social, ethical, economic, and technological factors. NRC has recommended that regulatory agencies take steps to establish and maintain a clear conceptual distinction between risk assessment and risk management (15). Different risk management approaches are taken by different regulatory agencies, depending largely on the kind of exposure being evaluated and the agency's statutory authority. The three most common risk management approaches mandated by the various environmental and public health laws are risk only, risk balancing (risk-benefit), and technological control (25), Public perceptions may also influence risk management decisions.

A regulatory decision using the *risk only* approach takes into account only the level of risk that is considered necessary to protect public health. However, the *risk balancing* approach may consider

social, economic, and technological factors as well. This approach involves developing a consensus among interest groups and making trade-offs for the public well-being. The third risk management approach, *technological control,* involves reducing risk by applying the best available, most feasible technologies.

RISK ASSESSMENT AND NEUROTOXIC SUBSTANCES

The risk assessment approaches outlined above have been discussed extensively in various Federal and State regulations and guidance documents (see, e.g., 51 FR 33992-34003; 50 FR 10372-10442) (5), as well as in the scientific literature (50 FR 10372-10442) (15). Practical applications of these methods of risk assessment can be found in hundreds of regulations promulgated by EPA, the Food and Drug Administration, the Occupational Safety and Health Administration (OSHA), and the Consumer Product Safety Commission, as well as in the scientific literature. A representative sampling of the latter, and references to many more assessments, can be found in the National Academy of Sciences' series *Drinking Water and Health (8* volumes through 1988). While legitimate scientific differences exist regarding many issues in risk assessment, particularly those concerning extrapolation, consensus exists regarding the need for some type of analysis of the risk posed by toxic substances. Differences in approaches to risk assessment can result in different conclusions with respect to the degree of risk posed by a toxic substance and how much of society's resources should be used to address toxicological concerns.

To date, most risk assessments have been devoted to carcinogenic substances. As mentioned above, some basis has been found for development of explicit descriptions of noncarcinogenic risk, and most of the guidance documents mentioned above deal with this issue. There is some discussion of noncarcinogenic effects in the *Drinking Water and Health series* cited above, in EPA's Toxic Substances Control Act Test Guidelines (50 FR 39398-39418; 50 FR 39458-39470), and in various documents issued by the World Health Organization (28). EPA's "Guidelines for the Health Assessment of Suspected Developmental Toxicants," issued in 1986 (51 FR 34040), were the first noncancer risk assessment guidelines produced.

Risk assessment strategies were originally developed for evaluating carcinogens, which have often been viewed as exerting "all-or-none" effects (although this view is changing for some carcinogens). Neurotoxic substances differ from carcinogens in that adverse effects are strongly dependent on dose—severe effects may result from exposure to large concentrations of a substance, but little effect may result from exposure to low concentrations. Also, cancer is a relatively well-defined, discrete endpoint. Neurotoxicity may result in multiple endpoints (e.g., seizures, memory loss, hearing loss), thus complicating risk assessment strategies. In most of these cases, and in many specific regulatory applications, the RfD approach to risk characterization (or its equivalent in occupational settings) is accepted.

Examples of Regulatory Approaches

Federal regulatory agencies have not developed uniform risk assessment approaches to neurotoxic substances, although EPA has been particularly active in developing risk assessment guidelines (1 2). To illustrate how various agencies have used risk assessment, one may focus on four widely recognized neurotoxic substances: lead, ethyl-p-nitrophenyl phosphonothionate (EPN, an organophosphorous pesticide), acrylamide (a chemical often used because of its ability to polymerize), and n-hexane (a commonly used industrial solvent) (9). Each of these substances is representative of a major category of environmental exposure: lead (general exposure), EPN (pesticide), and acrylamide and n-hexane (occupational exposures).

Two of the four chemicals examined, EPN and n-hexane, are regulated primarily on the basis of neurotoxic concerns. Risk assessments for the two focus on histopathologica1 analyses, as opposed to examinations of functional effects. Lead is regulated because of its neurotoxic properties, especially prenatally and in early life, and its effects on the blood-forming system. Acrylamide is regulated because of both its carcinogenic and its neurotoxic potentials (box 7-E).

The methodological approaches used by EPA (for lead and EPN) and OSHA (for acrylamide and n-hexane) were generally the same. In identifying hazards, the agencies placed greatest reliance on human data, when they were available, but also relied on animal data. Principal emphasis was placed

Photo credit: National Arhives, EPA Documerica Collection

on identifying NOAELs and determining the appropriate margin of exposure for humans.

In determining the bases for the occupational standards, OSHA adopted the American Conference of Governmental Industrial Hygienists' (ACGIH) threshold limit values (TLVs) for the n-hexane and acrylamide standards. ACGIH documented its derivation of each TLV (l), but the relationships between the TLVs and the underlying documentation were not explicitly stated. EPA's standards were stated more clearly.

A detailed evaluation of the risk assessment information used in the development of the standards for lead, EPN, acrylamide, and n-hexane confirmed that the safety factor approach has been used for neurotoxicity risk assessment in diverse circumstances. The safety factor approach (based on a NOAEL) is commonly used in the U.S. pharmaceutical industry, where neurotoxic effects sometimes limit the dose (10).

To date, there have been few instances in which neurotoxicity was the *principal* basis for regulation. There are perhaps three reasons for this. First, toxicity tests currently used by regulatory agencies are generally not specifically designed to identify neurotoxic agents. Histopathological analyses may identify some neurotoxic agents, but pathological analyses alone are of limited use in identifying adverse effects on the function of the nervous system (e.g., behavioral effects). Second, the risk assessment methodologies currently in use for carcinogenesis assume the absence of a threshold, whereas those used for other toxic effects assume a threshold. The practical consequence of this dichotomous system is that whenever a toxic agent exhibits both carcinogenic and other-than-carcinogenic effects, concerns about the carcinogenic risks tend to override concerns about other risks that may be associated with the agent at low doses. As indicated earlier, however, these assumptions regarding thresholds for carcinogenic and other toxic chemicals are the subject of debate. Third, in some cases other, noncancer health effects may occur at lower levels than neurotoxic effects, and regulations may have been based on these concerns.

Concerns about carcinogenicity have dominated discussions about the risks posed by toxic substances. However, the adverse effects on organs and organ systems (the nervous system, liver, immune system, cardiovascular system, and so on) may pose an equal or greater threat to public health. Consequently, it is important to devise risk assessment strategies to address noncancer health risks.

Limitations of Current Approaches

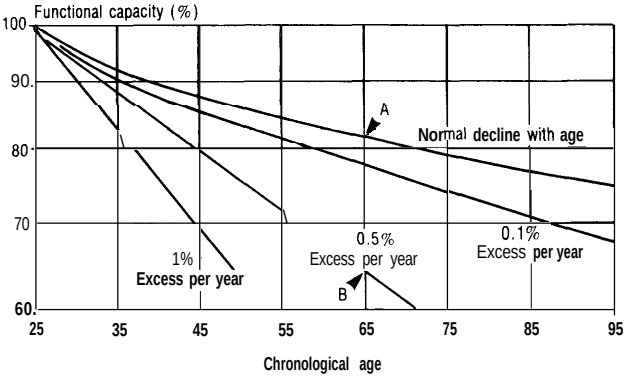
The nervous system is perhaps the most complex organ system of the body. Consequently, evaluating the neurotoxic potential of environmental agents is a particular challenge. For example, testing for a toxic effect on one component of the nervous system (e.g., hearing) may or may not reveal a toxic effect on another component (e.g., vision); furthermore, an effect on one nervous system function is not necessarily predictive of an effect on another nervous system function. Other factors that complicate risk assessment of neurotoxic substances include the apparent reversibility of many neurotoxic effects and the possibility of "silent," or latent, adverse

effects, which become apparent only late in life (27) (see box 7-G).

An important difference between neurotoxicity and carcinogenicity is the extent to which the effects are reversible. The endpoint of carcinogenicity is considered to be irreversible (although some persons argue that, strictly speaking, a "cure" would render the effect reversible), whereas the endpoints of neurotoxicity may be either reversible or irreversible, depending on the specific effect, the duration and frequency of exposure, and the toxicity of the substance (see box 7-G). Reversibility requires the introduction of a new variable into the risk assessment equation. Consequently, it has been proposed that it may be useful to specify a reversible effect level (27). Yet, determining whether or not an effect is truly reversible can be difficult. For example, exposure to a neurotoxic substance early in life could appear to give rise to a short-term, reversible effect, but later in life an irreversible effect (e.g., a neurological disease) could become apparent.

The age at which neurotoxic effects are evaluated can strongly influence the outcome of a risk analysis. For example, mice exposed to methylmercury during prenatal development may not exhibit adverse effects until late in their lives (23). Similarly, humans exposed to a toxic substance early in life may not suffer adverse effects until decades later. With age, the functional capacity of the brain declines significantly, and chronic exposure to some neurotoxic substances is thought to accelerate this process (27). As indicated in the hypothetical example in figure 6-4, a small acceleration in the loss of functional capacity may, with time, have very significant effects. For example, in this model, the postulated functional capacity of the brain that has not been chronically exposed to neurotoxic substances through age 65 is more than 80 percent of the capacity at age 65 (see figure 6-4, point A). However, even a modest acceleration of 0.5 percent per year results in a functional capacity of 65 percent (see point B), a more than 15-point reduction in this theoretical example. As figure 6-4 suggests, an acceleration of 1.0 percent per year could result in a large reduction in functional capacity over time. Hence, many scientists and regulatory officials believe that risk analyses should consider adverse effects over a range of ages and should take into account possible latent effects (27). More research is needed to understand the actual relationship between decline in functional capacity and the impact of toxic substances on the nervous system.

Figure 6-4-Postulated Decline in Brain Functional Capacity With Age and Exposure to Neurotoxic Substances



The heavy line (top) shows the rate posited to occur without added variables. The lighter lines show accelerations of 0.1 percent, 0.5 percent, and 1.0 percent annually, as might be produced by chronic exposure to neurotoxic substances.

SOURCE: B. Weiss and W, Simon, "Quantitative Perspectives on the Long-Term Toxicity of Methyl Mercury and Similar Poisons," ***Behavioral Toxicology,*** B. Weiss and V. Laties (eds.) (New York, NY: Plenum Press, 1975).

Issues in Hazard Identification

Neurotoxicological assessment of environmental agents is not uniform among Federal regulatory agencies (1 1,20,24). Although hazard identification through general toxicity testing (described inch. 5) can identify substances with *obvious* neurotoxic properties, substances producing more subtle effects are generally not detected. One exception is EPA's Office of Toxic Substances, which has included a battery of more sophisticated neurotoxicity tests in its regulatory requirements (see ch. 7). Until recently, however, EPA has not imposed these specific test requirements on many substances.

As discussed in chapter 5, neurotoxicity tests (and toxicity tests in general) should meet certain criteria such as sensitivity, specificity, and reproducibility before being adopted for routine use in hazard identification or dose-response assessment. Currently, there is a consensus among scientists that several neurotoxicological tests meet the necessary criteria and could be used for routine testing of potentially neurotoxic substances (14,18,22). A question that remains is precisely how EPA will use test data in the regulatory decisionmaking process.

Issues in Dose-Response Assessment

Thresholds and the RfD Approach-Toxic agents are conventionally classified into two groups: those that exert adverse effects only after a threshold dose is exceeded and those that theoretically increase risk at all doses greater than zero (no-threshold agents). This classification system, which has important consequences for risk assessment, has the practical effect of grouping all carcinogens into the no-threshold category and all other forms of toxicity into the threshold category. As indicated earlier, there is uncertainty about whether all carcinogens belong in the no-threshold group and all noncarcinogens, including neurotoxic agents, belong in the threshold group (19).

One consequence of this dichotomous system is that different models for risk assessment are used for the two groups. Typically, noncarcinogenic risk is modeled under the assumption that risk declines with dose and that the mathematical model that describes this relationship applies even below the region of observed effects. The model used for carcinogens yields zero risk (zero probability of developing cancer) only when the dose becomes zero. On the other hand, the consequence of assuming a threshold model is the development of RfDs by applying safety factors to NOELs or NOAELs.

NOAEL v. NOEL-The objective of using a NOAEL as opposed to a NOEL, as described above, is to establish a threshold dose such that no *adverse* effect would be likely to occur at exposures at or below this dose. Implicit in the establishment of a NOAEL is the understanding that any effects that occur below this dose would have no known biological relevance, whereas effects occurring above this dose would be harmful. A NOEL, on the other hand, reflects a dose below which no observable effect of any type occurs. An effect might be measurable, yet not be deleterious to human health; in fact, the effect might be beneficial or might not be biologically meaningful.

Due to limits in scientific understanding of the biological relevance of measurable effects, regulatory standards are often based on NOELs and not NOAELs. This reflects the intent to err on the side of caution and to be overprotective rather than underprotective of public health. When regulating pharmaceuticals, NOAELs are used because *adverse* effects must be distinguished from positive pharmacological effects. Also, recent draft developmental toxicity testing guidelines (54 FR 13472; 53 FR 5932; 51 FR 17890) are based on the NOAEL. Developmental testing is discussed in chapter 5.

Photo credit: United Automobile, Aerospace, and Agricultural Implement Workers of America-U4VPublic Relations Department

Safety Factors—A safety factor, as described above, is generally applied to the NOEL or NOAEL to estimate the RfD. However, the use of such factors creates an uncertainty in itself. Safety factors are generally derived not from chemical-specific data, but from *a priori* estimations of the ranges of variation in extrapolations used to determine an RfD (from animals to humans and within the human population). The limited research done on the topic of safety factors needed to account for intraspecies variability indicates that the tenfold factor used for this purpose tends to be more rather than less protective of a diverse human population (7,26).

What is unclear at the present time is the actual degree of protection against toxic effects that is associated with the RfD. It is likely that different safety factors are necessary for different chemicals; thus the RfD may be highly protective for one neurotoxic substance (i.e., one associated with an extremely low risk) but insufficiently protective for another.

Issues in Risk Characterization

Uncertainty-An important component of risk characterization that often receives inadequate attention is the delineation of uncertainties in the various stages of the assessment. The greater the total uncertainty, the less likely it is that the calculated risk represents the true risk. Every risk characterization should include a thorough discussion of all the uncertainties (50 FR 10372-10442, 51 FR 33992-34003).

There are uncertainties inherent in every risk assessment. Some are fundamental scientific questions common to all risk assessments. Questions that often arise include:

- How useful are animals as predictors of human toxicity?
- How well do responses at high doses predict responses at low doses?
- What is the relative importance of individual v. social risk? (See box 6-A.)

These questions are often difficult to answer; indeed, at times they cannot be answered. In the meantime, assumptions must be made and mathematical and interpretational conventions must be devised. In some areas, such as high to low dose extrapolation, there is no consensus among scientists. Regulatory agencies deal with such situations by adopting science policy assumptions (15). These assumptions tend to favor overstatement of risk, a practice that agencies justify on public health grounds.

Other types of uncertainties arise because the data available for any given risk assessment are incomplete or imperfect. Examples of these kinds of uncertainties include the following questions: Are toxic responses resulting from different experimental exposure routes comparable? What environmental concentrations of a contaminant are people actually exposed to? Is the toxic substance chemically modified in the environment or metabolized in the body to a more or less active form? What quantity of the chemical actually reaches and causes the toxic effect in the target organ?

Assumptions must be made to fill these gaps in information. The risk assessor usually tries to be conservative by making a worst probable case assumption. This results in a final risk number that, although uncertain, is highly likely to overestimate the true risk.

SUMMARY AND CONCLUSIONS

Toxicology and risk assessment have traditionally dealt with effects that can be characterized by *physical* changes, including morphological or biochemical abnormalities. Functional impairment of the organism, such as a chemically induced change in behavior, is now also considered a direct and measurable consequence of these types of abnormalities. The relationship between pathological changes and functional impairment needs to be further correlated, however.

Determining the biological mechanisms underlying behavior is a frontier of basic research. Research aimed at defining adverse effects at the cellular and systems levels is being actively pursued in tandem with the development of toxicity testing methods. Several tests already developed in the academic, regulatory, and private sectors can be used in routine preliminary or secondary screening of neurotoxic substances. Regulatory agencies will most likely adopt a tiered testing approach[2] whenever specific neurotoxicity tests as well as general toxicity tests are required.

With respect to identifying neurotoxic hazards and developing standardized methods of predicting them, several approaches might be pursued simultaneously. Research to improve the utility of structure-activity relationships in predicting neurotoxicity is critically needed. Strong, continuing research programs are needed to further refine and validate neurotoxicity tests. To guide the direction of this research, specific epidemiological surveillance programs could be developed to follow subpopulations that are exposed to high concentrations of neurotoxic substances (e.g., certain occupational groups). Also, weight-of-evidence approaches for classifying neurotoxic hazards, similar to EPA's weight-of-evidence classification scheme for carcinogens, might help guide regulatory decisionmaking. EPA has recently proposed such a scheme for neurotoxicity.

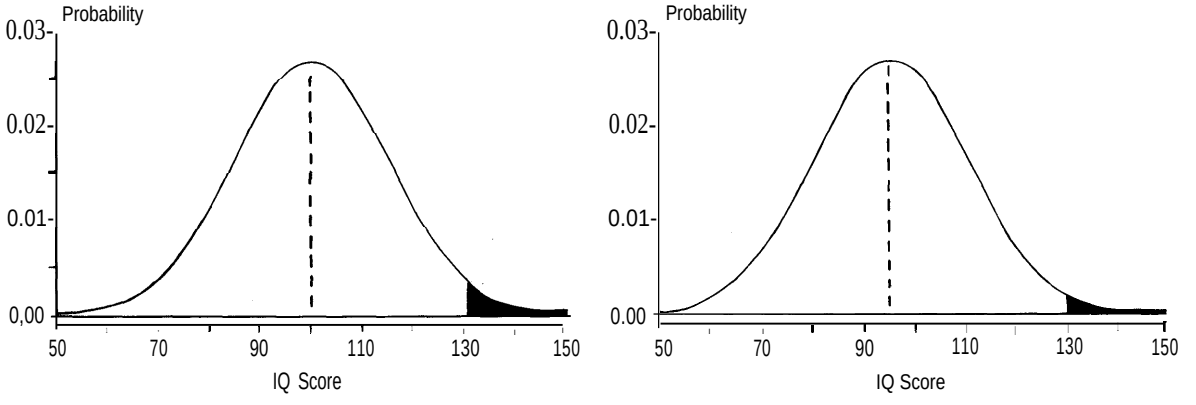
Further exploration of the scientific basis for the threshold assumption now adopted for all noncarcinogens is needed. The desirability of adopting nonthreshold dose-response relationships for some agents

[2]The tiered testing approach is described in ch. 5.

Box 6-A—Individual v. Social Risks

Risk, particularly as it relates to carcinogenicity, is typically evaluated in the context of the individual, but evaluations of this kind may underestimate the overall risk to society. A useful example is levels of lead in children. A recent analysis of lead levels in newborns grouped concentrations of lead in the umbilical cord into three categories: low (1.8 micrograms of lead per deciliter of blood, ug/dl), medium (6.5 ug/dl), and high *(14.5* ug/dl). Even though children in the high exposure group fell just below the 15 ug/dl level considered to be hazardous (according to the Centers for Disease Control), at age 2 these children score 8 percent lower than nonexposed children on a standard mental development index (the Mental Development Index of the Bayley Scales of Infant Development).

Although individual children do not display adverse neurotoxic effects, the impacts on society can be very significant. As shown in the figure below, a 5 percent reduction in the mean scores can result in a significantly different distribution of IQ scores.



Distributions of intelligence test scores. Left: standardized mean 100; standard deviation 15. Right: mean 95.

The graph on the left indicates a typical distribution, in which the mean IQ score is 100 (the standardized average). In a population of 100 million, 2.3 million individuals would be expected to score above 130. In the distribution on the right, based on a mean score of 95, about 1 million individuals score above 130, a reduction of 1.3 million individuals. Clearly, what may appear to be small differences in lead leve1-differences that are not apparent in individual evaluations-can translate into a major social problem, detectable only through statistical analysis of data from exposed and unexposed children.

SOURCE: Adapted from B. Weiss, ''Neurobehavioral Toxicity as a Basis for Risk Assessment,'' ***Trends in Pharmacological Sciences 9:59-62, 1988.***

producing delayed, irreversible neurotoxic effects might be considered. Alternative means of modeling dose-response relationships for neurotoxic agents need to be investigated and developed into practical tools. If the safety factor approach is to be maintained, empirical verifications of its adequacy are desirable, not only for neurotoxic agents but for other toxic agents as well. In addition, methods are needed to identify relatively weak neurotoxic chemicals that can cause adverse effects in humans after low-level exposures over long periods of time. Facilitating and maintaining coordination among researchers and scientists in the various regulatory programs will be crucial to ensure efficient and consistent integration of research findings into regulatory decisionmaking.

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