National Research Council: Risk assessment in the Federal Government: Managing the process. National Academy Press, Washington DC, 1983

I
The Nature of Risk Assessment

Recent criticisms of the conduct and use of risk assessment by regulatory agencies have led to a wide range of proposed remedies, including changes in regulatory statutes and the development of new methods for assessing risk. The mandate to this Committee was more limited. Our objective was to examine whether alterations in institutional arrangements or procedures, particularly the organizational separation of risk assessment from regulatory decision-making and the use of uniform guidelines for inferring risk from available scientific information, can improve federal risk assessment activities.

Before undertaking to determine whether organizational and procedural reforms could improve the performance and use of risk assessment in the federal government, the Committee examined the state of risk assessment and the regulatory environment in which it is performed. In this chapter, we define risk assessment and differentiate it from other elements in the regulatory process, analyze the types of judgments made in risk assessment, and examine its current government context. Because one chronic health hazard, cancer, was highlighted in the Committee's congressional mandate and has dominated public concern about public health risks in recent years, most of our report focuses on it. Furthermore, because activities in four agencies--the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the Occupational Safety and Health Administration (OSHA), and the Consumer Product Safety Commission (CPSC)--have given rise to many of the proposals for changes in risk assessment practices, our review focuses on these four agencies. The conclusions of this report, although directed primarily at risk assessment of potential carcinogens as performed by these

four agencies, may be applicable to other federal programs to reduce health risks.

TERMINOLOGY

Despite the fact that risk assessment has become a subject that has been extensively discussed in recent years, no standard definitions have evolved, and the same concepts are encountered under different names. The Committee adopted the following terminology for use in this report.

RISK ASSESSMENT AND RISK MANAGEMENT

We use risk assessment to mean the characterization of the potential adverse health effects of human exposures to environmental hazards. Risk assessments include several elements: description of the potential adverse health effects based on an evaluation of results of epidemiologic, clinical, toxicologic, and environmental research; extrapolation from those results to predict the type and estimate the extent of health effects in humans under given conditions of exposure; judgments as to the number and characteristics of persons exposed at various intensities and durations; and summary judgments on the existence and overall magnitude of the public-health problem. Risk assessment also includes characterization of the uncertainties inherent in the process of inferring risk.

The term risk assessment is often given narrower and broader meanings than we have adopted here. For some observers, the term is synonymous with quantitative risk assessment and emphasizes reliance on numerical results. Our broader definition includes quantification, but also includes qualitative expressions of risk. Quantitative estimates of risk are not always feasible, and they may be eschewed by agencies for policy reasons. Broader uses of the term than ours also embrace analysis of perceived risks, comparisons of risks associated with different regulatory strategies, and occasionally analysis of the economic and social implications of regulatory decisions--functions that we assign to risk management.

The Committee uses the term risk management to describe the process of evaluating alternative regulatory actions and selecting among them. Risk management, which is carried out by regulatory agencies under various legislative

mandates, is an agency decision-making process that entails consideration of political, social, economic, and engineering information with risk-related information to develop, analyze, and compare regulatory options and to select the appropriate regulatory response to a potential chronic health hazard. The selection process necessarily requires the use of value judgments on such issues as the acceptability of risk and the reasonableness of the costs of control.

STEPS IN RISK ASSESSMENT

Risk assessment can be divided into four major steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. A risk assessment might stop with the first step, hazard identification, if no adverse effect is found or if an agency elects to take regulatory action without further analysis, for reasons of policy or statutory mandate.

Of the four steps, hazard identification is the most easily recognized in the actions of regulatory agencies. It is defined here as the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition (cancer, birth defect, etc.). It involves characterizing the nature and strength of the evidence of causation. Although the question of whether a substance causes cancer or other adverse health effects is theoretically a yes-no question, there are few chemicals on which the human data are definitive. Therefore, the question is often restated in terms of effects in laboratory animals or other test systems, e.g., "Does the agent induce cancer in test animals?" Positive answers to such questions are typically taken as evidence that an agent may pose a cancer risk for any exposed humans. Information from short-term in vitro tests and on structural similarity to known chemical hazards may also be considered.

Dose-response assessment is the process of characterizing the relation between the dose of an agent administered or received and the incidence of an adverse health effect in exposed populations and estimating the incidence of the effect as a function of human exposure to the agent. It takes account of intensity of exposure, age pattern of exposure, and possibly other variables that might affect response, such as sex, lifestyle, and other modifying factors. A dose-response assessment usually

requires extrapolation from high to low dose and extrapolation from animals to humans. A dose-response assessment should describe and justify the methods of extrapolation used to predict incidence and should characterize the statistical and biologic uncertainties in these methods.

Exposure assessment is the process of measuring or estimating the intensity, frequency, and duration of human exposures to an agent currently present in the environment or of estimating hypothetical exposures that might arise from the release of new chemicals into the environment. In its most complete form, it describes the magnitude, duration, schedule, and route of exposure; the size, nature, and classes of the human populations exposed; and the uncertainties in all estimates. Exposure assessment is often used to identify feasible prospective control options and to predict the effects of available control technologies on exposure.

Risk characterization is the process of estimating the incidence of a health effect under the various conditions of human exposure described in exposure assessment. It is performed by combining the exposure and dose-response assessments. The summary effects of the uncertainties in the preceding steps are described in this step.

The relations among the four steps of risk assessment and between risk assessment and risk management are depicted in Figure I-1. The type of research information needed for each step is also illustrated.

SCIENTIFIC BASIS FOR RISK ASSESSMENT

Step 1. Hazard Identification

Although risk assessment as it is currently practiced by federal agencies for the estimation of carcinogenic risk contains several relatively new features, the scientific basis for much of the analysis done in risk assessment is well established. This is especially true of the first step in the assessment process, hazard identification. Four general classes of information may be used in this step: epidemiologic data, animal-bioassay data, data on in vitro effects, and comparisons of molecular structure.

Epidemiologic Data

Well-conducted epidemiologic studies that show a positive association between an agent and a disease are

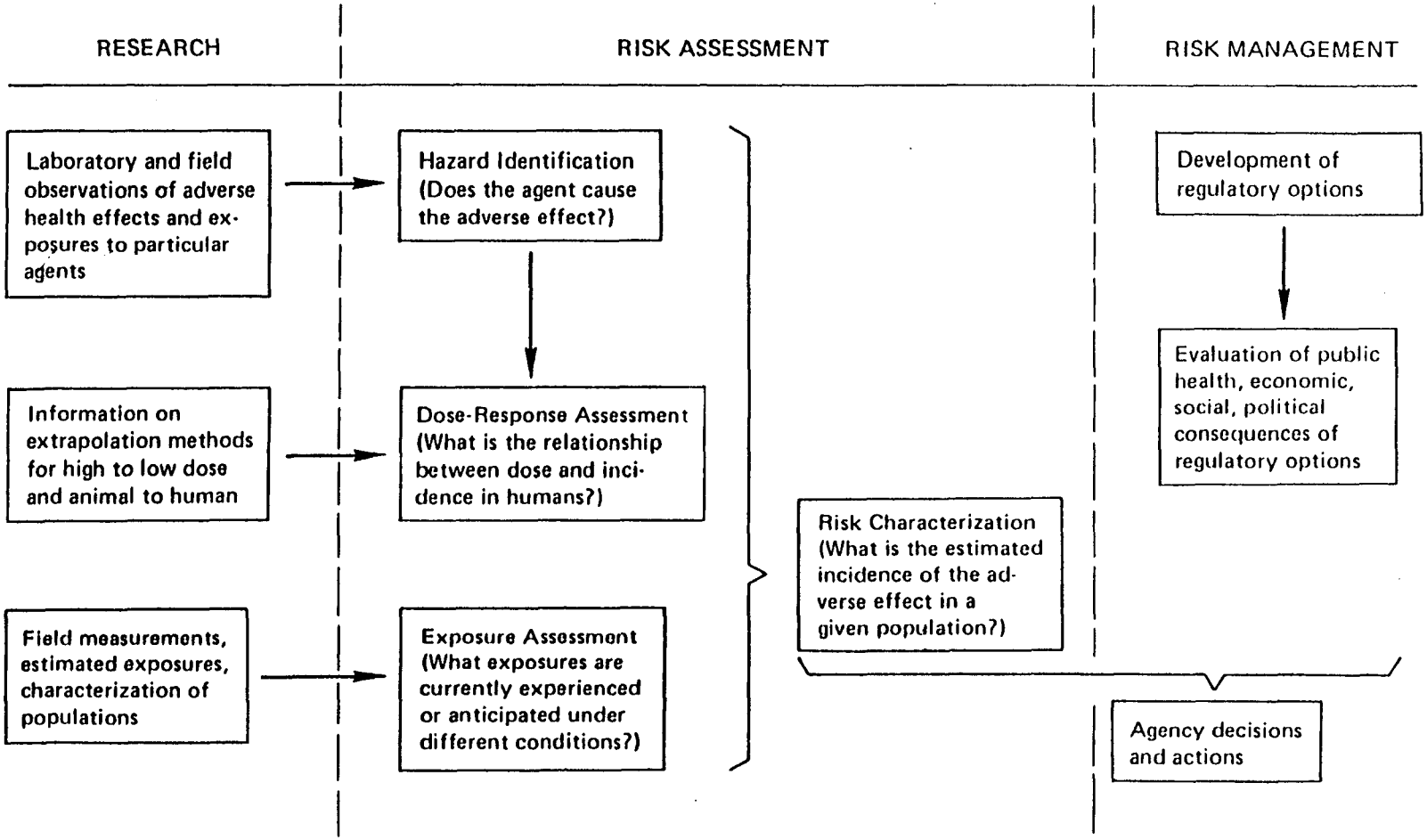

FIGURE I-1 Elements of risk assessment and risk management.

accepted as the most convincing evidence about human risk. This evidence is, however, difficult to accumulate; often the risk is low, the number of persons exposed is small, the latent period between exposure and disease is long, and exposures are mixed and multiple. Thus, epidemiologic data require careful interpretation. Even if these problems are solved satisfactorily, the preponderance of chemicals in the environment has not been studied with epidemiologic methods, and we would not wish to release newly produced substances only to discover years later that they were powerful carcinogenic agents. These limitations require reliance on less direct evidence that a health hazard exists.

Animal-Bioassay Data

The most commonly available data in hazard identification are those obtained from animal bioassays. The inference that results from animal experiments are applicable to humans is fundamental to toxicologic research; this premise underlies much of experimental biology and medicine and is logically extended to the experimental observation of carcinogenic effects. Despite the apparent validity of such inferences and their acceptability by most cancer researchers, there are no doubt occasions in which observations in animals may be of highly uncertain relevance to humans.

Consistently positive results in the two sexes and in several strains and species and higher incidences at higher doses constitute the best evidence of carcinogenicity. More often than not, however, such data are not available. Instead, because of the nature of the effect and the limits of detection of animal tests as they are usually conducted, experimental data leading to a positive finding sometimes barely exceed a statistical threshold and may involve tumor types of uncertain relation to human carcinogenesis. Interpretation of some animal data may therefore be difficult. Notwithstanding uncertainties associated with interpretation of some animal tests, they have, in general, proved to be reliable indicators of carcinogenic properties and will continue to play a pivotal role in efforts to identify carcinogens.

Short-Term Studies

Considerable experimental evidence supports the proposition that most chemical carcinogens are mutagens and that many mutagens are carcinogens. As a result, a positive response in a mutagenicity assay is supportive

evidence that the agent tested is likely to be carcinogenic. Such data, in the absence of a positive animal bioassay, are rarely, if ever, sufficient to support a conclusion that an agent is carcinogenic. Because short-term tests are rapid and inexpensive, they are valuable for screening chemicals for potential carcinogenicity and lending additional support to observations from animal and epidemiologic investigations.

Comparisons of Molecular Structure

Comparison of an agent's chemical or physical properties with those of known carcinogens provides some evidence of potential carcinogenicity. Experimental data support such associations for a few structural classes; however, such studies are best used to identify potential carcinogens for further investigation and may be useful in priority-setting for carcinogenicity testing.

Step 2. Dose-Response Assessment

In a small number of instances, epidemiologic data permit a dose-response relation to be developed directly from observations of exposure and health effects in humans. If epidemiologic data are available, extrapolations from the exposures observed in the study to lower exposures experienced by the general population are often necessary Such extrapolations introduce uncertainty into the estimates of risk for the general population. Uncertainties also arise because the general population includes some people, such as children, who may be more susceptible than people in the sample from which the epidemiologic data were developed.

The absence of useful human data is common for most chemicals being assessed for carcinogenic effect, and dose-response assessment usually entails evaluating tests that were performed on rats or mice. The tests, however, typically have been designed for hazard identification, rather than for determining dose-response relations. Under current testing practice, one group of animals is given the highest dose that can be tolerated, a second group is exposed at half that dose, and a control group is not exposed. (The use of high doses is necessary to maximize the sensitivity of the study for determining whether the agent being tested has carcinogenic potential.) A finding in such studies that increased exposure leads to an increased incidence has been used primarily

to corroborate hazard identification, that is, to show that the agent does indeed induce the adverse health effect.

The testing of chemicals at high doses has been challenged by some scientists who argue that metabolism of chemicals differs at high and low doses; i.e., high doses may overwhelm normal detoxification mechanisms and provide results that would not occur at the lower doses to which humans are exposed. An additional factor that is often raised to challenge the validity of animal data to indicate effects in man is that metabolic differences among animal species should be considered when animal test results are analyzed. Metabolic differences can have important effects on the validity of extrapolating from animals to man if, for example, the actual carcinogen is a metabolite of the administered chemical and the animals tested differ markedly from humans in their production of that metabolite. A related point is that the actual dose of carcinogen reaching the affected tissue or organ is usually not known; thus, dose-response information, of necessity, is based on administered dose and not tissue dose. Although data of these types would certainly improve the basis for extrapolating from high to low doses and from one species to another, they are difficult to acquire and often unavailable.

Regulators are interested in doses to which humans might be exposed, and such doses usually are much lower than those administered in animal studies. Therefore, dose-response assessment often requires extrapolating an expected response curve over a wide range of doses from one or two actual data points. In addition, differences in size and metabolic rates between man and laboratory animals require that doses used experimentally be converted to reflect these differences.

Low-Dose Extrapolation

One may extrapolate to low doses by fitting a mathematical model to animal dose-response data and using the model to predict risks at lower doses corresponding to those experienced by humans. At present, the true shape of the dose-response curve at doses several orders of magnitude below the observation range cannot be determined experimentally. Even the largest study on record--the ED_{01} study involving 24,000 animals--was designed only to measure the dose corresponding to a 1% increase in tumor incidence. However, regulatory agencies are often concerned about much lower risks (1 in 100,000 to 1

in 1,000). Several methods have been developed to extrapolate from high doses to low doses that would correspond to risk of such magnitudes. A difficulty with low-dose extrapolation is that a number of the extrapolation methods fit the data from animal experiments reasonably well, and it is impossible to distinguish their validity on the basis of goodness of fit. (From a mathematical point of view, distinguishing among these models on the basis of their fit with experimental data would require an extremely large experiment; from a practical point of view, it is probably impossible). As Figure I-2 shows, the dose-response curves derived with different models to diverge below the experimental doses and may diverge substantially in the dose range of interest to regulators. Thus, low-dose extrapolation must be more than a curve-fitting exercise, and considerations of biological plausibility must be taken into account.

Although the five models shown in Figure I-2 may fit experimental data equally well, they are not equally plausible biologically. Most persons in the field would agree that the supralinear model can be disregarded, because it is very difficult to conceive of a biologic mechanism that would give rise to this type of low-dose response. The threshold model is based on the assumption that, below a particular dose (the "threshold" dose of a given carcinogen) there is no adverse effect. This concept is plausible, but not now confirmable. The ED_{01} study showed an apparent threshold for bladder cancers caused by 2-acetylaminofluorene; when the data were replotted on a scale giving greater resolution (OTA, 1981), the number of bladder tumors consistently increased with dose, even at the lowest doses, and no threshold was detected. Another aspect of the debate over thresholds for inducing carcinogenic effects is the argument that agents that act through genotoxic mechanisms are not likely to have a threshold, whereas agents whose effects are mediated by epigenetic mechanisms are possibly more likely to have a threshold. The latter argument is also currently open to scientific challenge. Finally, apparent thresholds observable in animal bioassays cannot be equated with thresholds for entire populations. Even if a threshold exists for individuals, a single threshold would probably not be applicable to the whole population.

Animal-to-Human Dose Extrapolation

In extrapolating from animals to humans, the doses used in bioassays must be adjusted to allow for differ-

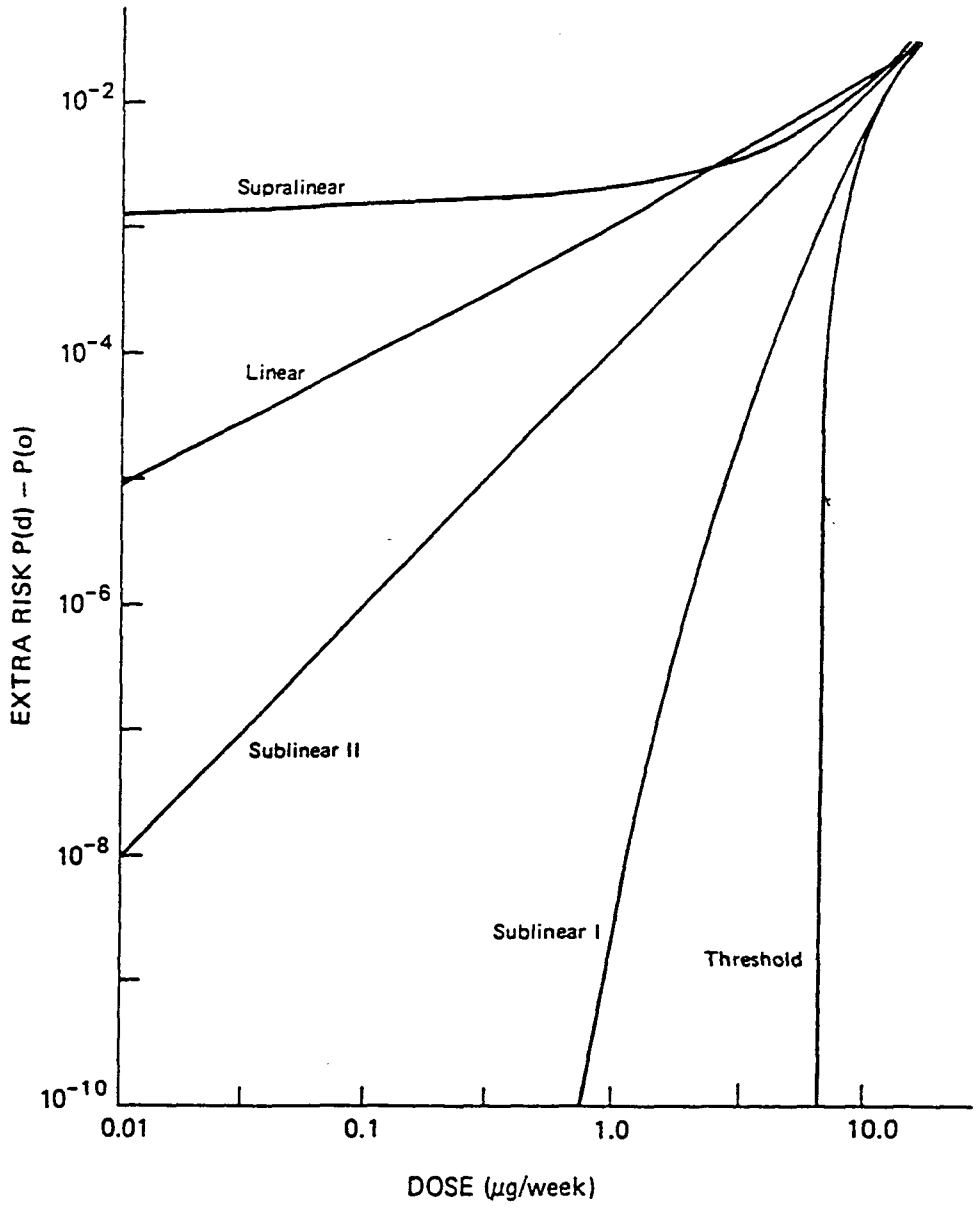

FIGURE I-2 Results of alternative extrapolation models for the same experimental data. NOTE: Dose-response functions were developed (Crump, in press) for data from a benzopyrene carcinogenesis experiment with mice conducted by Lee and O'Neill (1971).

ences in size and metabolic rates. Several methods currently are used for this adjustment and assume that animal and human risks are equivalent when doses are measured as milligrams per kilogram per day, as milligrams per square meter of body surface area, as parts per million in air, diet, or water, or as milligrams per kilogram per lifetime. Although some methods for conversion are used more frequently than others, a scientific basis for choosing one over the other is not established.

Step 3. Exposure Assessment

The first task of an exposure assessment is the determination of the concentration of the chemical to which humans are exposed. This may be known from direct measurement, but more typically exposure data are incomplete and must be estimated. Models for estimating exposure can be complex, even in the case of structured activity, as occurs in the workplace. Exposure measurements made on a small group (e.g., workers in a particular industrial firm) are often applied to other segments of the worker population.

Exposure assessment in an occupational setting consists primarily of estimation of long-term airborne exposures in the workplace. However, because an agent may be present at various concentrations in diverse occupational settings, a census of exposures is difficult and costly to conduct. In the community environment, the ambient concentrations of chemicals to which people may be exposed can be estimated from emission rates only if the transport and conversion processes are known. Alternative engineering control options require different estimates of the reduction in exposure that may be achieved. For new chemicals with no measurement data at all, rough estimations of exposure are necessary. Some chemical agents are of concern because they are present in foods or may be absorbed when a consumer product is used. Assessments of exposure to such agents are complicated by variations in diet and personal habits among different groups in the population. Even when the amount of an agent in a food can be measured, differences in food storage practices, food preparation, and dietary frequency often lead to a wide variation in the amount of the agent that individuals ingest. Patterns of use affect exposure to many consumer products; for example, a solvent whose vapor is potentially toxic may be used outdoors or it may be used in a small, poorly ventilated room, where the concentration of vapor in the air is much higher.

Another important aspect of exposure assessment is the determination of which groups in the population may be exposed to a chemical agent; some groups may be especially susceptible to adverse health effects. Pregnant women, very young and very old people, and persons with impaired health may be particularly important in exposure assessment. The importance of exposures to a mixture of carcinogens is another factor that needs to be considered in asssing human exposures. For example, exposure to cigarette smoke and asbestos gives an incidence of cancer that is much greater than anticipated from carcinogenicity data on each substance individually. Because data detecting such synergistic effects are often unavailable, they are often ignored or accounted for by the use of various safety factors.

Step 4. Risk Characterization

Risk characterization, the estimate of the magnitude of the public-health problem, involves no additional scientific knowledge or concepts. However, the exercise of judgment in the aggregation of population groups with varied sensitivity and different exposure may affect the estimate.

SCIENTIFIC AND POLICY JUDGMENTS IN RISK ASSESSMENT

The uncertainties inherent in risk assessment can be grouped in two general categories: missing or ambiguous information on a particular substance and gaps in current scientific theory. When scientific uncertainty is encountered in the risk assessment process, inferential bridges are needed to allow the process to continue. The Committee has defined the points in the risk assessment process where such inferences must be made as components. The judgments made by the scientist/risk assessor for each component of risk assessment often entail a choice among several scientifically plausible options; the Committee has designated these inference options.

COMPONENTS OF RISK ASSESSMENT

A list of components in carcinogenicity risk assessments was compiled by the Committee and is given below. This

list is not exhaustive or comprehensive, nor would all components listed be found in every risk assessment. The actual array of components in a particular risk assessment depends on a number of factors, including the types and extent of available data.

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 finding in 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? Is a 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 vastly different 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 follow-up 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 unequivocally related to exposure, or should they apply to all types of cancers?
- How should exposures to other carcinogens, 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 (in 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?

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 pollutants into the atmosphere due to convection, wind currents, etc., or predict seepage rates of toxic chemicals into soils and groundwater?
- How should dietary 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?

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

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 will the uncertainties be described to agency decision-makers?
- Which dose-response assessments and exposure assessments should be used?
- Which population groups should be the primary targets for protection, and which provide the most meaningful expression of the health risk?

THE INTERPLAY OF SCIENCE AND POLICY IN RISK ASSESSMENT

A key premise of the proponents of institutional separation of risk assessment is that removal of risk assessment from the regulatory agencies will result in a clear demarcation of the science and policy aspects of regulatory decision-making. However, policy considerations inevitably affect, and perhaps determine, some of the choices among the inference options. To examine the types of judgments required in risk assessment, the Committee has analyzed several components and the inference options for each.

Hazard Identification

The Committee has identified 25 components in hazard identification. These components differ in a number of ways. However, two major differences germane to the question considered here are the degree of scientific uncertainty encountered in each and the effect of choosing different inference options on the outcome of the risk assessment. Consider the following examples.

One component of risk assessment is the decision as to whether to use experimental animal data to infer risks to humans. Although data from studies of rats and mice may not always be predictive of adverse health effects in humans, the scientific validity of this approach is widely accepted. The use of positive animal data is the more conservative choice for this component. The use of

negative animal data to determine the absence of carcinogenic risk is less conservative, especially when the sensitivity of the assay is low. (The Committee uses the term conservative with appropriate modifiers to describe the degree to which a particular inference option for components in hazard identification will increase the likelihood that a substance will be judged to be a significant hazard to human health).

A component about which there is considerably more scientific uncertainty than the preceding example is the question of whether to count all types of benign tumors as evidence of carcinogenicity. Some benign tumors probably can progress to malignant lesions and some probably do not. The judgment that benign tumors and malignant tumors should be counted equally will affect tumor incidence and may influence the yes-no determination in hazard identification, and it can also affect the dose-response relation by increasing incidence at the doses tested. Thus, counting benign tumors is often the more conservative approach.

The examples just given differ in the degree to which scientific understanding can inform the judgments to be made. They are similar, however, in that for each, the available inference options differ in conservatism. For many components, this difference in degree of conservatism among plausible inference options is not as clear as in the preceding examples and depends on the data available on a given substance. For example, the decision to combine incidences for all tumor types and calculate an overall tumor incidence can influence the final yes-no decision in hazard identification. However, in this case, whether such a choice is more conservative than not combining incidences depends on the incidences for each tumor type in test and control animals. If the incidence in control animals is slightly below the incidences in test animals for all tumor types and individual differences are not statistically significant, combining all tumor types would be more conservative. However, if incidences show no consistent trend and differences are statistically significant for only one tumor type, combining the tumors would be less conservative.

Dose-Response Assessment

The Committee has identified 13 components of dose-response assessment. Two major components are high- to low-dose extrapolation and interspecies dose conversion.

In a recent NRC report on the health effects of nitrate, nitrite, and N-nitroso compounds (National Academy of Sciences, 1981), three extrapolation models (the one-hit model, the multistage model, and the multihit model) were used to estimate the dose of a carcinogenic nitrosamine (dimethylnitrosamine) needed to cause cancer in one of a million rats. The doses calculated were 0.03 parts per billion (one-hit), 0.04 ppb (multistage), and 2.7 ppb (multihit); that is, the risk estimate per unit of dose would be lower for the one-hit and multistage models than for the multihit model for this experiment.

Other judgments in dose-response assessment that will affect the final estimate include choice of the experimental data set (from among many that might be available) to be used to calculate the relation between dose and incidence of tumors (e.g., use of the most sensitive animal group will result in the most conservative estimate), choice of a scaling factor for conversion of doses in animals to humans (the risks calculated can vary by a factor of up to 35, depending on the method used), and the decision of whether to combine tumor types in determining incidence (as mentioned earlier, the decision to lump tumors might be more or less conservative than the decision not to combine incidences from different tumor types).

Exposure Assessment

Discussion of specific components in exposure assessment is complicated by the fact that current methods and approaches to exposure assessment appear to be medium- or route-specific. In contrast with hazard identification and dose-response assessment, exposure assessment has very few components that could be applicable to all media. For example, a model describing transport of a chemical through the atmosphere is necessarily quite different from a model describing transport through water or soil, whereas the use of a particular dose-response extrapolation model in dose-response assessment is independent of the medium or route of exposure. In any event, an assessor has several options available for estimating exposure to a particular agent in a particular medium, and these options will yield more or less conservative estimates of exposure. Among the options are different assumptions about the frequency and duration of human

exposure to an agent or medium, rates of intake or contact, and rates of absorption.

Risk Characterization

The final expressions of risk derived in this step will be used by the regulatory decision-maker when health risks are weighed against other societal costs and benefits to determine an appropriate action. Little guidance is available on how to express uncertainties in the underlying data and on which dose-response assessments and exposure assessments should be combined to give a final estimate of possible risk.

Basis for Selecting Inference Options

The Committee has presented some of the more familiar, and possibly more controversial, components of risk assessment. A review of the list of components reveals that many components lack definitive scientific answers, that the degree of scientific consensus concerning the best answer varies (some are more controversial among scientists than others), and that the inference options available for each component differ in their degree of conservatism. The choices encountered in risk assessment rest, to various degrees, on a mixture of scientific fact and consensus, on informed scientific judgment, and on policy determinations (the appropriate degree of conservatism).

That a scientist makes the choices does not render the judgments devoid of policy implications. Scientists differ in their opinions of the validity of various options, even if they are not consciously choosing to be more or less conservative. In considering whether to use data from the most sensitive experimental animals for risk assessment, a scientist may be influenced by the species, strains, and gender of the animals tested, the characteristics of the tumor, and the conditions of the experiment. A scientist's weighting of these variables may not easily be expressed explicitly, and the result is a mixture of fact, experience (often called intuition), and personal values that cannot be disentangled easily. As a result, the choice made may be perceived by the scientist as based primarily on informed scientific judgment. From a regulatory official's point of view, the same choice

may appear to be a value decision as to how conservative regulatory policy should be, given the lack of a decisive empirical basis for choice.

A risk assessor, in the absence of a clear indication based on science, could choose a particular approach (e.g., the use of an extrapolation model) solely on the basis of the degree to which it is conservative, i.e., on the basis of its policy implications. Furthermore, a desire to err on the side of overprotection of public health by increasing the estimate of risk could lead an assessor to choose the most conservative assumptions throughout the process for components on which science does not indicate a preferred choice. Such judgments made in risk assessment are designated risk assessment policy, that is, policy related to and subservient to the scientific content of the process, in contrast with policy invoked to guide risk management decisions, which has political, social, and economic determinants.

When inference options are chosen primarily on the basis of policy, risk management considerations (the desire to regulate or not to regulate) may influence the choices made by the assessors. The influence can be generic or ad hoc; i.e., assessments for all chemicals would consistently use the more or less conservative inference options, depending on the overall policy orientation of the agency ("generic"), or assessments would vary from chemical to chemical, with more conservative options being chosen for substances that the agency wishes to regulate and less conservative options being chosen for substances that the agency does not wish to regulate. (The desire to regulate or not would presumably stem from substance-specific economic and social considerations.) The possible influence of risk management considerations, whether real or perceived, on the policy choices made in risk assessment has led to reform proposals (reviewed later in this report) that would separate risk assessment activities from the regulatory agencies.

Table I-1 recapitulates the terms introduced in this discussion.

RISK ASSESSMENT IN PRACTICE

This section addresses past agency practices of risk assessment associated with efforts to regulate toxic substances.

TABLE I-1 Summary of Terms

Risk Assessment. Risk assessment is the qualitative or quantitative characterization of the potential health effects of particular substances on individuals or populations.

Risk Management. Risk management is the process of evaluating alternative regulatory options and selecting among them. A risk assessment may be one of the bases of risk management.

Steps. Risk assessments comprise many or all of the following steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization.

Components. Steps in risk assessment comprise many components--points in a risk assessment at which judgments must be made regarding the analytic approach to be taken.

Inference options. For many components, two or more inference options are available.

Risk Assessment Policy. Risk assessment policy consists of the analytic choices that must be made in the course of a risk assessment. Such choices are based on both scientific and policy considerations.

RISK ASSESSMENT AND REGULATORY DECISION-MAKING

The regulatory process can be initiated in many ways. Each regulatory agency typically has jurisdiction over a large number of substances, but circumstances force an allocation of resources to a few at a time. The decision as to which substances to regulate is based, at least in part, on the degree of hazard. Thus, some notion of relative hazard (implicit or explicit, internally generated or imposed by outside groups) is necessary. Critics of federal regulation have contended that the agencies have not set their priorities sensibly. In general, agency risk assessments for priority-setting have been more informal, less systematic, and less visible than those for establishing regulatory controls.

Agenda-setting involves decisions about which substances should be selected (and often in what order) for more intense formal regulatory review. All programs face this problem, but it assumes different configurations: some programs cover a finite and known set of chemicals that must be reviewed, so the order of the regulatory reviews is the key question, and the primary job of the risk assessor is to help the agency implement a worst-first approach. For example, EPA's pesticides program has long had lists of suspect pesticide ingredients, and agency officials have had to decide which ones warrant formal consideration of cancellation or of new controls. An agency's agenda may also respond to private-sector initiatives (in the case of approval of new drugs or pesticides), conform to statutory directives, or react to new evidence of hazards previously unrecognized or thought to be less serious. This agenda formation phase, too, involves elements of risk assessment by the agency, the Congress, or private-sector entities; that is, there must be some assessment, however informal, that indicates reason for concern.

For many items on an agency's regulatory agenda, hazard identification alone will support a conclusion that a chemical presents little or no risk to human health and should be removed from regulatory consideration, at least until new data warrant renewed concern. If a chemical is found to be potentially dangerous in the hazard-identification step, it could then be taken through the steps of dose-response assessment, exposure assessment, and risk characterization. At any of these steps, the evaluation might indicate that a substance poses little or no risk and therefore can be removed from regulatory consideration until new data indicate a need for reevaluation.

Chemicals that are judged to present appreciable risks to health are candidates for regulatory action, and an agency will begin to develop options for regulating exposures. Regulatory options usually involve specific product or process changes and typically need to be based on extensive engineering and technical knowledge of the affected industry. Evaluation of the regulatory options includes recomputation of the predicted risk, in accord with altered expectations of exposure intensity or numbers of persons exposed.

Many of the activities of regulatory agencies do not conform to this sequential approach. However, regardless of the sequence of steps and the number of steps used to

determine whether regulatory action is warranted, risk assessment serves at least two major functions in regulatory decisions: first, it provides an initial assessment of risks, and, if the risk is judged to be important enough to warrant regulatory action, it is used to evaluate the effects of different regulatory options on exposure. In addition, it may be used to set priorities for regulatory consideration and for further toxicity testing.

These varied functions place different requirements on risk assessors, and a single risk assessment method may not be sufficient. A risk assessment to establish testing priorities may appropriately incorporate many worst-case assumptions if there are data gaps, because research should be directed at substances with the most crucial gaps; but such assumptions may be inappropriate for analyzing regulatory controls, particularly if the regulator must ensure that controls do not place undue strains on the economy. In establishing regulatory priorities, the same inference options should be chosen for all chemicals, because the main point of the analysis is to make useful risk comparisons so that agency resources will be used rationally. However, this approach, which may be reasonable for priority-setting, may have to yield to more sophisticated and detailed scientific arguments when a substance's commercial life is at stake and the agency's decision may be challenged in court. Furthermore, the available resources and the resulting analytic care devoted to a risk assessment for deciding regulatory policy are likely to be much greater for analyzing control actions for a single substance than for setting priorities.

THE AGENCIES THAT REGULATE

The approach to risk assessment varies considerably among the four federal agencies. Differences stem primarily from variations in agency structure and differences in statutory mandates and their interpretation.

Organizational Arrangements

The Food and Drug Administration (FDA) is a component of the Department of Health and Human Services, whose Secretary is the formal statutory delegate of the powers exercised by FDA. FDA is headed by a single official,

the Commissioner of Food and Drugs, who is appointed by and serves at the pleasure of the Secretary of the Department of Health and Human Services. It is organized in product-related bureaus, each of which employs its own scientists, technicians, compliance officers, and administrators. FDA has a long (75-year) and strong scientific tradition. According to a recent Office of Technology Assessment summary, FDA had taken or proposed action on 24 potential carcinogens by 1981.

Like FDA, the Environmental Protection Agency (EPA) is headed by a single official, but EPA's Administrator is appointed by the President subject to Senate confirmation. Also like FDA, EPA resembles a confederation of relatively discrete programs that are coordinated and overseen by a central management. The agency was established in 1970, but many of its programs (e.g., air and water pollution control and pesticide regulation) predate its formation and previously were housed in and administered by other departments. Other programs, such as those for toxic substances and hazardous waste, are rather new. EPA's research, policy evaluation, and, until recently, enforcement efforts were separated organizationally from the program offices that write regulations. EPA has had the widest experience with regulating carcinogens; as of 1981, it had acted on 56 chemicals in its clean-water program, 29 in its clean-air program, 18 in its pesticide program, and two in its drinking-water program.

The Occupational Safety and Health Administration (OSHA) is part of the Department of Labor. The agency's head is an Assistant Secretary of Labor, who requires Senate confirmation. Although FDA and EPA derive their scientific support largely from their own full-time employees, until the late 1970s OSHA relied on other agencies, primarily the National Institute of Occupational Safety and Health, an agency of the Department of Health and Human Services. This division reflects a conscious congressional choice in 1970 to place the health experts on whom OSHA was expected to rely in an outside environment believed more congenial to scientific inquiry and less vulnerable to political influence. As of 1981, 18 potential carcinogens had been acted on by OSHA.

The Consumer Product Safety Commission (CPSC) enforces five statutes, including the Consumer Product Safety Act and the Federal Hazardous Substances Act. Both empower CPSC to regulate unreasonable risks of injury from products used by consumers in the home, in schools, or in

recreation. The much smaller CPSC differs sharply from the other three agencies in two important respects: it does not have a single administrative head, but instead is governed by five Commissioners, who can make major regulatory decisions only by majority vote; and the Commissioners are appointed for fixed terms by the President with Senate confirmation. Before 1981, CPSC had acted on five potential carcinogens.

The four agencies have attempted to coordinate risk assessment activities in the past, most notably through the Interagency Regulatory Liaison Group (IRLG), which formed a work group on risk assessment to develop a guideline for assessing carcinogenic risks. Assisted by scientists from the National Cancer Institute and the National Institute for Environmental Health Sciences, it examined the various approaches used by the four agencies to evaluate evidence of carcinogenicity and to assess risk. The IRLG (1979a,b) then integrated and incorporated these evaluative procedures into a document, "Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks," which described the basis for evaluation of carcinogenic hazards identified through epidemiologic and experimental studies and the methods used for quantitative estimation of carcinogenic risk.

Regulatory Statutes*

Examination of the statutes that the four agencies administer reveals important differences in the standards that govern their decisions. The Office of Technology Assessment has summarized (Table I-2) statutes that pertain to the regulation of carcinogenic chemicals. In particular, the statutes accord different weights to such criteria as risk, costs of control, and technical feasibility. In addition, different modes of regulation vary in their capacity to generate the scientific data necessary to perform comprehensive risk assessments.

Several laws require agencies to balance regulatory costs and benefits. Examples of balancing provisions are found in the Safe Drinking Water Act; the Federal Insecticide, Fungicide, and Rodenticide Act; the Toxic Substances

*This discussion draws heavily on the Office of Technology Assessment report, Technologies for Determining Cancer Risks from the Environment, 1981.

Control Act; and the section on fuel additives in the Clean Air Act. Under such provisions, a risk assessment can be used to express the nature and extent of public-health benefits to be attained through regulation.

Some regulatory programs involve the establishment of technology-based exposure controls. This approach is followed, for example, in portions of the clean-water program and the part of the hazardous-wastes program that deals with waste-incineration standards. In such programs, a risk assessment may be used to show the human exposure that corresponds to a specific degree of risk or to calculate the risk remaining after control technologies are put in place.

Some statutes mandate control techniques to reduce risks to zero whenever hazard is affirmed. Such techniques include outright bans of products, as envisioned in the Delaney clause in the Federal Food, Drug, and Cosmetic Act. In addition, if the concept of a threshold below which carcinogens pose no risk is not accepted, strict interpretations of ample margin of safety language in federal clean-air and clean-water legislation would require that exposures to carcinogenic pollutants be reduced to zero. The role of risk assessment in cases where mandatory control techniques must reduce risks to zero may be simply to affirm that a hazard exists.

The difference between programs that involve premarketing approval of substances and programs that operate through post hoc mechanisms, such as environmental emission limits, may have an important influence over the quality of risk assessments. The most important effect of this difference may lie in the fact that premarketing approval programs (such as those for pesticides, for new human drugs, and for new food additives) empower an agency to require the submission of sufficient data for a comprehensive risk assessment, whereas other programs tend to leave agencies to fend for themselves in the acquisition of necessary data.

There can be little question that differing statutory standards for decision affect the weight that agencies accord risk assessments. Like differences in the mode of regulation, they probably have affected the rigor and scope of many assessments. If risk is but one of several criteria that a regulator must consider or if data are expensive to obtain, it would not be surprising if an agency devoted less effort to risk assessment. However, the Committee has not discovered differences in existing statutes that should impede the adoption of uniform,

TABLE I-2 . Public Laws Providing for the Regulation of Exposures to Carcinogens

Legislation (Agency)	Definition of toxics or hazards used for regulation of carcinogens	Degree of protection	Agents regulated as carcinogens (or proposed for regulation)	Basis of the legislation	Remarks
Federal Food, Drug and Cosmetic Act: (FDA)					
Food	Carcinogenicity for *additive* defined by Delaney Clause	No risk permitted, ban of additive	21 food additives and colors	Risk	
	Contaminants	"necessary for the protection of public health. . ." sec. 406 (346)	Three substances—aflatoxin, PCBs, *nitrosamines*	Balancing	
Drugs	Carcinogenicity is defined as a risk	Risks and benefits of drug are balanced.	Not determined	Balancing	
Cosmetics	"substance injurious under conditions of use prescribed."	Action taken on the basis that cosmetic is adulterated.	Not determined	Risk. No health claims are allowed for "cosmetics." If claims are made, cosmetic becomes a "drug."	
Occupational Safety and Health Act (OSHA)	Not defined in Act (but OSHA Generic Cancer Policy defines carcinogens on basis of animal test results or epidemiology.)	"adequately assures to the extent feasible that no employee will suffer material impairment of health or functional capacity. . ." sec. 6(b) (5)	20 substances	Technology (or balancing)	
Clean Air Act (EPA)					
Sec. 112 (stationary sources)	"an air pollutant. . . which . . . may cause, or contribute to, an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness." sec. 112(a) (1)	"an ample margin of safety to protect the public health. . ." sec. 112(b) (1) (B)	Asbestos, beryllium, mercury, vinyl chloride, benzene, radionuclides, and arsenic (an additional 24 substances are being considered)	Risk	Basis of the Airborne Carcinogen Policy

Sec. 202 (vehicles)	"air pollutant from any . . . new motor vehicles . . . or engine, which . . . cause, or contribute to, air pollution which may reasonably be anticipated to endanger public health or welfare." sec. 202A(a) (1)	"standards which reflect the greatest degree of emission reduction achieveable through . . . technology . . . available . . ." sec. 202(b) (3)(a) (1)	Diesel particulates standard	Technology Sec. 202(b) (4) (B) includes a risk-risk test for deciding between pollutant that might result from control attempts.	Sec. 202(b) (4) (A) specifies that no pollution control device, system, or element shall be allowed if it presents an unreasonable risk to health, welfare or safety.
Sec. 211 (fuel additives)	Same as above (211(c) (1)).	Same as above (211(c) (2) (a)).		Balancing. Technology-based with consideration of costs, but health-based in requirement that standards provide ample margin of safety.	A cost-benefit comparison of competing control technologies is required.
Clean Water Act (EPA) Sec. 307	Toxic pollutants listed in Committee Report 95-30 of House Committee on Public Works and Transportation. List from consent decree between EDF, NRDC, Citizens for Better Environment and EPA.	Defined by applying BAT economically achieveable (sec. 307(a) (2)), but effluent levels are to "provide(s) an ample margin of safety." (sec. 307(a) (4))	49 substances listed as carcinogens by CAG.	Technology	
Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Environmental Pesticide Control Act (EPA)	One which results in "unreasonable adverse effects on the environment or will involve unreasonable hazard to the survival of a species declared endangered . . ."	Not specified.	14 rebuttable presumptions against registrations either initiated or completed; nine pesticides voluntarily withdrawn from market.	Sec. 2(bb) Balancing: "unreasonable adverse effects . . ."	"Unreasonable adverse effects" means "unreasonable risk to man or the environment taking into account the economic, social, and environmental costs and benefits . . ."

TABLE I-2 (Continued)

Legislation (Agency)	Definition of toxics or hazards used for regulation of carcinogens	Degree of protection	Agents regulated as carcinogens (or proposed for regulation)	Basis of the legislation	Remarks
Resource Conservation and Recovery Act (EPA)	One which "may cause, or significantly contribute to an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness; or, pose a...hazard to human health or the environment..." sec. 1004(5) (A) (B)	"that necessary to protect human health and the environment..." sec. 3002-04	74 substances proposed for listing as hazardous wastes	Risk. The Administrator can order monitoring and set standards for sites.	
Safe Drinking Water Act (EPA)	"contaminant(s) which...may have an adverse effect on the health of persons." sec. 1401(1) (B)	"to the extent feasible...(taking costs into consideration)..." sec. 1412(a) (2)	Trihalomethanes, chemicals formed by reactions between chlorine used as disinfectant and organic chemicals. Two pesticides and 2 metals classified as carcinogens by CAG, but regulated because of other toxicities.	Balancing	
Toxic Substances Control Act (EPA)					
Sec. 4 (to require testing)	substances which "may present an unreasonable risk of injury to health or the environment." sec. 4(a) (1) (A) (i)	Not specified.	Six chemicals used to make plastics pliable.	Balancing: "unreasonable risk"	
Sec. 6 (to regulate)	substances which "present(s) or will present an unreasonable risk of injury to health or the environment." sec. 6(a)	"to protect adequately against such risk using the least burdensome requirement" sec. 6(a)	PCBs regulated as directed by the law.	Balancing: "unreasonable risk."	

Sec. 7 (to commence civil action against imminent hazards)	"Imminently hazardous chemical substance or mixture means a... substance or mixture which presents an imminent and unreasonable risk of serious or widespread injury to health or the environment."	Based on degree of protection in sec. 6			
Federal Hazardous Substances Act (CPSC)	"any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness..." 15 USC sec.	"establish such reasonable variations or additional label requirements... necessary for the protection of public health and safety..." 15 USC sec.		Risk	"Highly toxic" defined as capacity to cause death, thus toxicity may be limited to acute toxicity.
Consumer Product Safety Act (CPSC)	"products which present unreasonable risks of injury...in commerce," and " 'risk of injury' means a risk of death, personal injury or serious or frequent injury." 15 USC sec. 2051 "imminently hazardous consumer product' means consumer product which presents imminent and unreasonable risk of death, serious illness or severe personal injury." 15 USC sec. 2061	"standard shall be reasonably necessary to prevent or reduce an unreasonable risk of injury." 15 USC sec. 2056	Five substances: asbestos, benzene, benzidine (and benzidine-based dyes and pigments), vinyl chloride, "tris"	Balancing: "unreasonable"	Standards are to be expressed, wherever feasible, as performance requirements.

SOURCE: Office of Technology Assessment, Technologies for Determining Cancer Risks from the Environment, 1981.

government-wide risk assessment guidelines. Indeed, it is not satisfied that there are legal bases for inter-agency differences in the performance--as distinct from the use--of risk assessment for chronic health hazards.

CONCLUSIONS

On the basis of a review of the nature and the policy context of risk assessment, the Committee has drawn the following general conclusions:

1. Risk assessment is only one aspect of the process of regulatory control of hazardous substances. Therefore, improvements in risk assessment methods cannot be assumed to eliminate controversy over federal risk management decisions.

Restrictive regulation has seemed onerous to manufacturers, distributors, and users of products judged useful and valuable; conversely, inaction and delay with respect to regulatory proceedings have appeared callous and irresponsible to others. These dissatisfactions have been manifested in many ways, including criticism of risk assessment processes. The Committee believes that much of this criticism is inappropriately directed and gives rise to an unrealistic expectation that modifying risk assessment procedures will result in regulatory decisions more acceptable to the critics. Certainly risk assessment can and should be improved, with salutary effects on the appropriateness of regulatory decisions. However, risk management, although it uses risk assessment, is driven by political, social, and economic forces, and regulatory decisions will continue to arouse controversy and conflict.

2. Risk assessment is an analytic process that is firmly based on scientific considerations, but it also requires judgments to be made when the available information is incomplete. These judgments inevitably draw on both scientific and policy considerations.

The primary problem with risk assessment is that the information on which decisions must be based is usually inadequate. Because the decisions cannot wait, the gaps in information must be bridged by inference and belief, and these cannot be evaluated in the same way as facts. Improving the quality and comprehensiveness of knowledge is by far the most effective way to improve risk assess-

ment, but some limitations are inherent and unresolvable, and inferences will always be required. Although we conclude that the mixing of science and policy in risk assessment cannot be eliminated, we believe that most of the intrusions of policy can be identified and that a major contribution to the integrity of the risk assessment process would be the development of a procedure to ensure that the judgments made in risk assessments, and the underlying rationale for such judgments, are made explicit.

3. Two kinds of policy can potentially affect risk assessment: that which is inherent in the assessment process itself and that which governs the selection of regulatory options. The latter, risk management policy, should not be allowed to control the former, risk assessment policy.

Risk management policy, by its very nature, must entail value judgments related to public perceptions of risk and to information on risks, benefits, and costs of control strategies for each substance considered for regulation. Such information varies from substance to substance, so the judgments made in risk management must be case-specific. If such case-specific considerations as a substance's economic importance, which are appropriate to risk management, influence the judgments made in the risk assessment process, the integrity of the risk assessment process will be seriously undermined. Even the perception that risk management considerations are influencing the conduct of risk assessment in an important way will cause the assessment and regulatory decisions based on them to lack credibility.

4. Risk assessment suffers from the current absence of a mechanism for addressing generic issues in isolation from specific risk management decisions.

Although the practice of risk assessment has progressed in recent years, there is currently no mechanism for stimulating and monitoring advances on generic questions in relevant scientific fields or for the timely dissemination of such information to risk assessors.

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