RISK MANAGEMENT OF CARCINOGENS: INTEGRATION OF SCIENCE, LAW AND VALUES*

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ABSTRACT

Public policy emphasis on carcinogenesis stems from the complex nature of the diseases, the limited scientific theory, the variety of possible causes, and the frequency of occurrence. One of the several societal approaches focuses on understanding chemical causation and resultant preventive strategies. This approach depends on leading-edge scientific research and testing to identify and estimate causative agents, dose response relationships and environmental occurrence. Resultant control strategies must conform to the complex of applicable laws and a number of cultural values.

An orderly process of risk assessment, the scientific component, should precede the integration of other values in making a risk management decision. Risk assessment involves several sequential steps, is multi-disciplinary in nature, and is optimized through peer review.

Establishing priorities for information collection and evaluation is important because of the limited resources available for the complex processes leading to risk management decisions and resultant exposure control programs. Timeliness of the decision process is enhanced by early initiation of fact-finding to place risk, economic and social impacts into perspective. (These are relevant decision-assisting methodologies).

Achieving credibility in risk management decisions is often difficult. Soundness of the scientific data base, eminence of the assessors, and a clear delineation of the factors considered in arriving at the decision enhance credibility.

KEY WORDS

Risk Assessment
Risk Management
Carcinogenic Agents
Peer Review
Exposure Assessment

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I. INTRODUCTION - A BRIEF BACKGROUND ON CANCER AND CARCINOGENS

It seems appropriate that the risk management of carcinogens should be addressed in this workshop. This is not because the risk management of carcinogenic agents is so much different from the management of other hazards, but because debate on the extent of carcinogenic risk, along with public fear of the cancer diseases, results in much public policy attention to carcinogenic risk factors.

The term "cancer" refers to a very loose grouping of some 100 diseases, including such diverse types as the leukemias, the respiratory cancers, and angiosarcoma of the liver. In most cases the mechanism(s) of disease causation is not known, although important fragments of mechanistic information are being gained by the extensive current research.

The science of chemically induced carcinogenesis is barely two decades old and this may well explain the lack of underlying theory on mechanism and causation. On the other hand, the past twenty years have produced an ever-expanding body of empirical information coming from epidemiology, animal bioassay experiments, in vitro and in vivo "short-term" tests for mutagenicity, and a large body of basic research and clinical observations. Consequently, society has had a massive infusion of fragments of information without an underlying theoretical base. Cancer treatment and cancer prevention strategies thus rely partly on policy choices of professionals and governments.

As a matter of background perspective, cancer is the second most common terminal disease in the U.S., accounting for 20 to 25% of deaths. The number of cases of cancer has increased over the years. This is because cancer is primarily a disease of the older adult population; more people are living longer today largely as a result of significant reductions in the infectious diseases (such as tuberculosis, diphtheria, pneumonia, smallpox and polio). In order to make comparions of the rate of cancer mortality between populations groups, and to evaluate cancer trends, epidemiologists usually correct for age and calculate "age-adjusted" statistics.

Comprehensive statistics on cancer have been kept in the U.S. since 1930. These data show that the trend for major types of cancer have been rather steady, or declining in some instances. (1) There is one exception: respiratory cancer has been steadily rising. This is attributable primarily to increased cigarette smoking.

There seems to be general acceptance that at least 75 to 80% of cancers are attributable to extrinsic factors -- that is factors related to life style and the environment -- and that the remainder are due to hereditary factors. A 1982 study by a panel of experts of the National Academy of Sciences suggested that diet is a major cause of cancer. (2) An extensive study by Doll and Peto (3) investigated the various causes of cancer. Their findings are summarized in Table I.

Although carcinogenic agents associated with industrial activities constitute a relatively small proportion of the factors causing the cancer diseases, much government and corporate attention is directed to testing, evaluation and control of these agents.

During the past decade much has been written on a variety of potential carcinogenic agents such as vinyl chloride, benzene, bischloromethyl ether, polychlorinated biphenyl, DDT, saccharin, nitrite, and on and on.

An examination of the scientific literature shows that 26 substances have been linked to <u>human</u> cancer and that more than 2,000 substances have been identified as possible carcinogens in <u>animal</u> bioassay studies. It is further estimated that positive results for some 10,000 substances have been reported from the more than 100 short term test methods available to the laboratory scientists. These include a large number of substances occurring naturally in a variety of foodstuffs. The substances identified as active at <u>some</u> dose in <u>some</u> test system touch every facet of our lives. For example, even oxygen has been identified as a mutagen.

One of the best summaries of the state-of-the-art of carcinogenesis was recently published in draft form by the U.S. Office of Science and

Technology Policy (OSTP). (4) A select committee of government scientists developed this document. The spectrum of topics is illustrated in Table II, a condensation of chapter titles and major subtopics.

Government bodies in various nations (e.g., the National Toxicology Program in the U.S.) and international organizations (e.g., the International Agency for Research on Cancer (IARC) sponsored by the United Nations World Health Organization) have attempted to classify carcinogens according to the weight of evidence supporting the findings of carcinogenicity or other criteria.

In reality, these classification schemes all relate primarily to the nature of the carcinogenic effect or the circumstances of use of (exposure to) the substance. There is currently only limited underlying theory relating mechanisms and relative activity of various substances. Thus, the risk management of carcinogens must be based on a rapidly expanding empirical data base at the leading edge of scientific endeavors.

II. DISTINGUISHING BETWEEN RISK ASSESSMENT AND RISK MANAGEMENT

Risk management of carcinogens is discussed in many arenas -- the scientific community, the risk management decision centers, the news media, and by individuals in making their life-style choices. Discussions focus on whether a substance is a carcinogen, the degree of the potential risk, and what should be done. Complex values, such as economics, personal choice, and life-style preferences, are superimposed on the scientific and public health considerations in these discussions.

The nature of discussion in the U.S. is reflected in the thinking of three prominent individuals, a judge, a scientist, and a regulator:

> Judge Bazelon, who has overseen many environmental lawsuits, stated, "In response to the public's often emotional response to risk, scientists are tempted to disguise controversial

> value decisions in the cloak of scientific objectivity, obscuring those decisions from political accountability." (5)
>
> Dr. Bruce Ames, in talking about pesticide residues, recently said, "Defending a carcinogen is like attacking motherhood.... But people need to know the real cancer causes are smoking and alcohol, not what they eat [trace pesticide residues] in their food." (6)
>
> And William Ruckelshaus, Administrator of the U.S. Environmental Protection Agency (EPA) in June 1983, in a speech before the National Academy of Sciences stated, "What we are studying at EPA is a system that will make it easier for the public to understand how [regulatory] decisions are made, will establish more consistent standards for assessing a broad range of environmental and public health risks and will enable us to successfully manage the progressively more sophisticated and subtle findings of science." (7)

It seems necessary to have a framework for thinking about the management of carcinogenic risks. This framework consists of an appropriate thought process for getting to the decision points of risk management, and thus enables orderly planning and execution of the support tasks. Thus, the U.S. is currently evolving toward a distinction between risk assessment and risk management.

Last year the National Academy of Sciences completed a study dealing with "institutional mechanisms that best foster a constructive partnership between science and government, mechanisms to insure that government regulations rest on the best available scientific knowledge and to preserve the integrity of scientific data and judgments in the

unavoidable collision of the contending interests that accompany most important regulatory decisions". (8) The study drew a sharp distinction between two important elements: risk assessment and risk management. The Academy definitions were:

- Risk assessment -- "the use of the factual base to define the health effects of exposure of individuals or populations to hazardous materials and situations".

- Risk management -- "the process of weighing policy alternatives and selecting the most appropriate regulatory action, integrating the results of risk assessment with engineering data and with social, economic and political concerns to reach a decision". (8)

Today a considerable body of the scientific and regulatory/legislative communities accept this distinction. The nature of risk management requires an interaction of risk assessment with the consideration of control alternatives but the risk assessment process should be kept independent of the broader risk management values. In practice, the conceptual distinction has not yet been achieved. Agency decision documents frequently still blend social policy values into the risk assessment.

Another way of contrasting the two elements is to state that risk assessment is an important input component for a risk management decision.

III. THE GENERAL FRAMEWORK FOR RISK ASSESSMENT

Risk assessment generally includes the following key components (8):

1) Hazard identification. The determination of whether a particular substance is or is not causally linked to a particular health effect.

2) Hazard assessment (dose/response assessment). This is a determination of the relation between levels (magnitude) of

exposure or insult and the probability of occurrence in humans of the health effects in question.

3) Exposure assessment. The determination of the extent of human exposure before or after application of a risk management decision (a risk reduction alternative).

4) Risk characterization. The description of the nature and often the magnitude of human risk including attendant uncertainty.

In the past few years there has been increasing attention to the process by which risk assessments are carried out, the nature of the judgmental considerations and the expression of uncertainties involved in the risk assessment. Several key process factors can be highlighted.

Risk Assessment is a Multi-disciplinary Process

For example, in evaluating a carcinogenic risk, important contributions should come from the areas of toxicology, epidemiology, clinical medicine, biostatistics and industrial hygiene or engineering.

Risk Assessment is a Staged Process

If the goal is to have a reasonable objective characterization of risk, it is useful to view the characterization as a sequential process involving:

1) Perception of risk.
2) Preliminary risk assessment.
3) Proposed fact collection and research program.
4) Peer review of the information gathering approach.
5) Implementation of fact collection and research.
6) Comprehensive risk assessment.
7) Peer review of the assessment.

Frequently a perception of risk can be evaluated on the basis of readily available information and experience. In many cases however the data are limited, resulting in the need for further fact collection, and perhaps research and testing.

It is important that when a comprehensive risk assessment is to be made as a basis for regulatory activity, all relevant data should be evaluated as input to the risk characterization.

Case-by-Case Analysis of Risks is Preferred Over Generic Classification Systems

During the late 1970s, there was considerable discussion of generic approaches to risk assessment. Recipe-like direction for interpreting scientific data was once advocated by several government agencies. These proposals took such forms as stating that one positive bioassay classifies a substance as a carcinogen or that a linear model should be used for extrapolating from high doses to low doses.

After several years of discussion, there has been an emerging agreement that such simplistic approaches are not productive because they almost always overstate the risks -- frequently by several orders of magnitude. (9) As a result, the National Academy of Sciences has recommended that policy inference guidelines might be developed which would suggest a guideline for considerations in the more than 50 sub-decisions involved in translating animal data to human hazard potentials. (8) The development of these guidelines has not occurred, but there is increasing recognition that a risk assessment should state the uncertainties and the assumptions made in developing the dose/response relationship.

Exposure Assessment Usually Involves Sub-sets of the Populations Exposed

Identification and assessment of exposure profiles is receiving increasing attention in U.S. regulatory circles. There now seems to be general agreement that an analysis should subdivide the exposed population into a number of population sub-groups. This was illustrated recently in an

EPA assessment document on formaldehyde (10) where more than 25 sub-groups potentially exposed to formaldehyde were delineated and exposure levels estimated for each sub-group.

Frequently it is necessary to define the population sub-groups by type of activity (e.g., polymerizer operators general population) and then to estimate a distribution gradient of concentration levels within each sub-group. Generally speaking, monitoring data is preferred over modeling estimates to characterize exposure levels.

Hazard or Dose Response Assessment Involves Experienced Judgment

Hazard assessment of carcinogens draws from a variety of experimental data and sometimes from epidemiological studies. Quality of the experimental data is not always good or particularly relevant. Protocol design in terms of the number of animals or the size of the epidemiological cohort determines the statistical power of results. The rigor of the pathological examination is critical. Maintenance of the health of the experimental animals and control of a host of other variables are necessary for a study to be of optimum quality. Scientists conducting a risk assessment must frequently choose between studies or weight the results from some studies more than the results from others. Experience with the results of other studies and an ability to judge the strength of the evidence and/or the consistency of the data as a whole are thus necessary parts of the hazard assessment.

In the area of traditional toxicology it has been customary to determine the no-effect level for a substance in the most relevant animal studies and then to apply a safety factor, frequently 100-fold, to this no-effect level and thus derive a "safe" level for the substance. Use of the 100-fold safety factor, in reality, is a risk management policy decision which has ensured the safety of the food supply very well.

With the lack of consensus on whether there are thresholds for carcinogens, the question of extrapolation to low doses is much more difficult. To some degree, risk assessment has been perceived as synonymous with a

numbers game of estimating probabilities. Numerous assessments express risks in terms of statistical probabilities, such as, 10^{-5}, 10^{-6}, etc. Statisticians have developed a large number of models to extrapolate to low doses. These models range from the linear-through-zero model to the multi-stage models to the log probit model. These models can give risk factors for a single substance which differ by several orders of magnitude. In the case of saccharin in soft drinks, the estimates differed by a million-fold.

Although not universally accepted, there seems to be an emerging consensus that interdisciplinary judgmental considerations should be a strong part of the hazard characterization and that mathematical models, if they are to be used, should have biological relevance and should only be a tool to assist informed judgment in arriving at the risk characterization.

Risk Assessment Must Reflect the Current State-of-the-Art of Carcinogenesis

As mentioned earlier, the U.S. Office of Science and Technology Policy has recently published a review of the science of carcinogenesis. (4) A list of 31 principles was derived from this review. These are useful in evaluating carcinogenic risk and in designing of experimental programs. (Appendix I)

The principles are carefully drawn to reflect current knowledge and provide some encouragement for utilization of new information as it becomes available. The principles are expected to be a guide to the regulatory agencies as they evolve their own practices and decisions. It appears that the general reaction of the scientific community is favorable to most of the principles; however, there is concern about an overemphasis on the use of mathematical models without consideration of biologically relevant factors. Particularly controversial is the use of the upper 95% confidence limit and thus the lack of focus on a display of most probable values and the upper and lower bounds of risk.

Peer Review of the Risk Assessment Builds Scientific Consensus

In practice, the idealized staged process of risk assessment described above is frequently not achieved because of institutional staffing deficiencies, the time involved in collecting information on a substance or its exposure profile, or because of the urgency in reaching a risk management decision. Peer review can take many forms and a few examples illustrate approaches taken in the U.S.

The EPA has a staff which prepares comprehensive hazard assessment documents. Upon completion, these are reviewed by a Science Advisory Board (SAB) panel consisting of ten to fifteen scientists from academia.

IARC, in preparing descriptive monographs on potential carcinogenic agents, relies on an expert staff to collect the literature on a substance and then convenes a panel of scientific experts to review the information and to classify the substance as to the weight of evidence that the substance might pose a carcinogenic risk.

As another example, the potential hazards of formaldehyde were reviewed in a consensus workshop. In this case, a government research agency (the National Center for Toxicological Research) convened a number of expert scientists from government, academia, industry and other public sectors. Concurrent meetings addressed such topics as bioassay data, metabolism and pharmacokinetics, and epidemiology. The proceedings from the workshop represented a thrust toward scientific consensus. A similar type of consensus workshop was sponsored by Rockefeller University on the potential hazards of dioxin in September, 1983.

Finally, it should be kept in mind that more traditional forms of scientific peer review are essential precursors to sound risk assessments. Presentation of the results of experimental studies at scientific meetings and the peer review that precedes their publication tend to upgrade the quality of the data base available for a risk assessment and frequently contribute useful interpretations.

IV. THE BASIC FRAMEWORK FOR RISK MANAGEMENT OF CARCINOGENS

Risk management decisions involve values and perceptions: risk, life-style choices, economics and social value judgments. The risk manager must deal with the values directed by law or tradition and with his relative perspective of these values. This section treats the direction provided by law and several decision-assisting methodologies which can provide perspective to the risk manager.

Risk management decisions relating to carcinogens are of course made by a variety of individuals and institutions. A person may consciously weigh cancer risk in determining his smoking or dietary choices, a physician makes a risk management decision in prescribing a therapeutic regime for a leukemia patient, corporations consider values in instituting engineering controls and governments reflect societal values in developing regulatory controls. Corporate decisions reflect many of the same considerations as those of governments. For purposes of this discussion, only risk management decisions of governmental institutions will be discussed. Further, the discussion will be confined to those decisions resulting in regulations or directives that are binding (in contrast to guidelines or recommendations which by design leave flexibility in interpretation to those affected).

Risk Management Directions Flowing from Law

Generally speaking, government approaches to risk management of carcinogens are carried out within the general context of laws designed with a broader scope or purpose -- safety of the food supply, safety and health in the workplace, or protection of the health and environment from toxic substances or pollutants.

More than 30 health and environmental laws have been enacted in the U.S. and a particular carcinogenic substance might be regulated under almost any of these laws. A tabulation of some of these laws is shown in Table III.

It is important to note that the directions for risk management are delineated in these laws and that the nature of the risk management decision varies from one statute to another.

For purposes of this discussion, we will direct our attention to four statutes: the Food, Drug and Cosmetic Act, the Occupational Safety and Health Act, the Federal Insecticide, Fungicide and Rodenticide Act (covering pesticides), and the Toxic Substances Control Act. These four laws illustrate differences in the style of risk management direction provided by our legislative body, and to some degree, represent an historical evolution of approaches to risk management.

The Food, Drug and Cosmetic Act is designed to insure the safety of the food supply and the integrity of drug and cosmetic products. Drugs are evaluated on the basis of the therapeutic benefits in relation to negative health impacts (side effects). This is largely a judgmental management decision of the risk-benefit type. Food additives, on the other hand, must meet a general safety requirement; however carcinogenic substances are a special exception. In 1958 the famous Delaney Amendment was adopted, which states that no substance should be added to food which has been shown to be carcinogenic in humans or in appropriate animal experiments. In the U.S., food additives include direct food additives such as preservatives, colorants and flavoring agents, as well as trace indirect additives which may result from unintentional addition to food in the course of good manufacturing practices. For example, migration of trace constituents from food packaging materials is covered by this provision of the law.

The Occupational Safety and Health Act became law in 1970. Under this law, toxic substances, including carcinogens, are to be controlled to give worker health protection to the maximum extent feasible. Carcinogenic substances are not expressly mentioned but are regulated as part of the general category of toxic substances.

The pesticide law provides for a balancing of the benefits of use of the pesticide with the health and environmental risks incurred in its use.

Generally speaking, this law is driven by a fairly high degree of public concern for safety. Unless a pesticide is deemed to be essential and there are no suitable substitutes for controlling a serious pest, rather stringent controls and restrictions are placed on the registration of pesticides with evidence of carcinogenicity.

The Toxic Substances Control Act was enacted in 1976 and basically provides that unreasonable risks will be controlled. There is no specific definition of unreasonable risk in the statute. Unreasonable risk is to be determined on a case-by-case basis by a balancing of risk, economic and social impacts. Risk management decision criteria for carcinogens are not singled out from other toxic substances; however, carcinogenic substances, along with mutagenic and reproductive agents, are to be given priority consideration in evaluation of potential risks.

In summary, one can see that the legal framework for risk management in the U.S. is varied, including the concepts of zero risk, risk benefit, feasibility and the balancing of risk, social and economic impacts. To some observers, this diversity is confusing. To others, the inconsistency seems illogical. In practice, however, two factors lead to a narrower range of risk management options than is apparent from the strict reading of the statutes. First, two court decisions have blunted the concept of absolute zero risk. Under the Delaney Amendment to the Food, Drug and Cosmetic Act, the concept of de minimis risk has emerged. The complete Latin phrase "de minimis non curat lex" translates to "the law does not concern itself with trifles". Although a de minimis risk or a de minimis quantity has not been defined, the thrust is to disregard trace quantities of carcinogens or diminishingly small risks in establishing food additive regulations. Similarly, in a court interpretation of a benzene rule, OSHA has been directed to concern itself only with significant risks, not insignificant risks. Again these terms are not defined but provide a conceptual cutoff for regulatory action and negate the zero risk concept.

At the other end of the spectrum where feasibility or economic impacts can be weighed under the laws, the U.S. culture is driven by a "prudent

public health protection" value system. Thus, there is some tendency to weight health risk factors to a greater extent than economic impact factors.

Vinyl chloride illustrates the directing influence of U.S. laws on risk management decisions. Vinyl chloride was identified as an animal and human carcinogen during the period 1973 to 1975. The U.S. regulations developed during 1974 and thereafter, are summarized in Table IV. The tabulation contrasts the feasibility approach for workplace concerns, banning where substitutes were available for certain uses, reliance on the de minimis concept for trace constituents in packaging materials, application of feasible technology for emission/discharge control, and availability of information for potential transportation hazards.

From the above contrast, it can be seen that the discretionary factors which can be considered in a risk management decision will be variable from law to law and that generally the complexity of the regulatory decision process will be greater under the balancing statutes than those statutes driven strictly by risk considerations.

Thus, in the following discussion of decision-assisting methodologies it should be kept in mind that their degree of utility will depend upon the statutory discretion given to the government agency.

Decision-Assisting Methodologies

Priority setting. Richard Denney, a former EPA deputy general counsel, made the statement that "what you regulate is more important than how you regulate." (11) This statement emphasizes the importance of setting priorities for risk management with regard to substances or practices which are to be considered for possible regulation. It is generally accepted that there are finite limits to the human and financial resources that can be devoted to research and testing of carcinogenic hazards and the imposition of exposure controls. U.S. laws have generally left considerable discretion to government agencies in selecting their research, testing and control priorities.

Although much has been written on establishing priorities, there is no uniform practice at either the research/testing stage or the control stage. Scoring and criteria systems have been proposed for testing. (12) Regulatory control priorities are frequently driven by new information, by news publicity and by Congressional oversight (which is frequently responsive to news publicity). In the past few years, provisions have been made in several laws to trigger activity on specific substances or types of activity. Citizens' petitions can also request an agency to initiate action such as that mentioned earlier in the Toxic Substances Control Act.

To the extent that agencies have discretion in setting their priorities, there is a tendency to give weight to hazard and exposure information which raise a concern above a general background level or to the same risk level as that identified in recent regulatory actions.

In the context of carcinogens, weight of the evidence for carcinogenicity, relative potency of a carcinogenic agent, and the wide-spread dissemination of a substance receive considerable weighting in priority setting.

Risk assessment. This topic has been discussed earlier as an important precursor to risk management decision making. It is mentioned here to emphasize its importance to, and interaction with, many of these other decision-assisting methodologies.

Relative risk. The concept of relative risk can be useful from two perspectives: the spectrum of carcinogenic risks and the broader perspective of risks incurred from other societal activities.

The range of relative risks is vast -- potency of carcinogens can differ by factors of more than a million. Aflatoxin B_1 causes liver cancer in rats at a concentration in the low parts per billion in the diet; on the other hand, 2,000 to 5,000 parts per million of safrole, a flavoring agent, are required to induce tumors. Thus, for comparable control

levels of the chemicals, the risk from Aflatoxin B_1 is much higher than from safrole.

Comparison of carcinogenic risks with other societal risks is not as difficult as might at first be thought. Most people are familiar with, or relate to, the risks associated with coal mining, the automobile, the airplane, differences in cosmic ray exposure at high altitudes compared to sea level (e.g., Denver and New York City), swimming, home accidents, and various common diseases. Fortunately, reliable statistics have been compiled by the National Consumer Product Safety Commission, the Occupational Safety and Health Administration and others. Carcinogenic risks of course cannot be estimated with the reliability achieved for statistical empirical experience. However, the carcinogenic risks qualitatively can be ranked among the other societal risks.

Assuming that risk for a chemical use can be quantified, its relative degree of risk can be positioned within the bench mark spectrums of several known chemical and societal risks shown in Table V. This methodology provides perspective for decision. However, it is not a complete formula for decision, since other values must be considered in almost every decision.

Economic/social impact analysis. Economic and social impacts are difficult to define and quantify. Economic impacts, if they are identified, can be expressed in terms of costs of control, less cost for treatment, changes in profitability or other financial measures. However, economic and social impacts have many diverse elements and can touch a much greater segment of society than those who may be directly exposed to a carcinogen or those who incur costs of control. Of the impacts, one can mention:

- Purchasing power
- Employment
- Security
- Freedom of choice
- Status/ego
- Peace of mind
- Health
- Convenience
- Availability of goods or services
- Self-esteem
- Effects of alternatives
- Nutrition
- Sanitation
- Retention of technology
- Gross National Product

Some of these impacts can be expressed in health units, some in economic units, and some in a subjective sense, such as the quality of life. Under the balancing statutes, it is important that all of the significant impacts be identified and either quantified or described in objective terms as input for the decision.

Cost effectiveness or risk/control cost/benefit analysis. (13) No consideration of a specific risk can by itself provide us with the kind of perspective we must have in order to assess which resources should be allocated for its management -- and to what extent. The costs and benefits of controls must be considered simultaneously with the measurement of risk.

Risk/benefit analysis applied to limiting exposure or emission of substances is a difficult and complex exercise, especially when the additional and necessary dimension of control cost is added to the analysis. All three of these factors are generally estimated with varying degrees of precision. Assuming that the components of risk, control cost and benefits can be identified and assessed -- a difficult exercise in itself -- the problem becomes very difficult for the regulator if all parts of the equation are not in the same units.

However, judicious use of the available quantified information can be helpful to the regulator considering various control options. The challenge is to use comparison of risks, benefits and costs, but to show their limitations clearly. Several examples will illustrate the type of modeling that should prove useful to the regulatory decision maker.

When only the classical risks (i.e., those from exposure or emission) are considered, the relationship between risk and cost of control is as shown in Figure 1. So long as the substance exists there is no absolute guarantee of zero exposure (and some argue that absolute zero risk therefore is not achievable). A defined zero risk can be extrapolated from high risk experience, limit of detectability, or some other method. Somewhere along this curve we pass through the conditions provided by installing the best practicable technology for control (BPT), and at some higher cost we would achieve those provided by the best available technology (BAT). If benefits are not to be considered, this curve permits an academic evaluation of risk reduction versus cost control.

Most attempts to assess benefits simultaneously along with risk and cost assume that benefits continue to increase as risk is lowered by more costly controls. The presumption is that these three factors relate, as in Figure 2.

If the effect of increased cost of control is assessed for all risks, we must consider the scenario shown in Table VI.

The reduction in risk from direct exposure to a factor will at some level of additional cost of control create risks that increase with greater control cost. This will probably begin shortly after the cost of BPT, and instead of the classical risk/cost relationship, shown in Figure 2, we have the one shown in Figure 3. In Figure 3, Curve A might represent a risk to continued employment as rising control costs force shutdowns, and Curve B might represent a risk to purchasing power, which diminishes as higher costs result in higher prices.

The implementation of control actions may involve other risks. For example, the accident rate in the construction industry suggests one fatality for a $36 million capital investment. Thus, the health risk component of a regulatory proposal needs to be adjusted by the risks introduced by the efforts to reduce the health risk. (The example is not atypical for such regulatory considerations as the EPA and OSHA deliberations on benzene and vinyl chloride. The regulatory proposals

for each of these chemicals required construction programs of several hundred million dollars with limited direct risk reductions.)

Consideration of control cost impact on all risks can cause the benefit curve of Figure 2 to peak and become more like the dashed curve of Figure 4, since in reality the "new" risks shown in the right-hand column of Table VI are a loss of benefit. Perhaps a simpler way to consider the entire equation is to recognize that some risks are loss of benefits, simplify the assessment to a risk/cost/risk analysis, and assess the composite risk -- including risk from exposure plus risk of loss of benefits -- to give a relationship, as shown in Figure 5. In such analysis, it will be extremely important to factor in the risks created by alternative factors or substances as increased cost of control creates a shift to alternatives.

Somewhere along the cost curve, probably soon after the cost of BPT is exceeded, we shift to a risk/risk analysis, as benefits change from positive to negative.

V. ARTICULATION AND COMMUNICATION OF THE RISK ASSESSMENT AND THE RISK MANAGEMENT DECISION

Risk management decisions are frequently highly controversial. Burden on the regulated industry can be high, facilities or research investment may have to be abandoned, or fears of incomplete health protection may not be allayed. Furthermore, the science and the web of interlocking values can be very, very complex.

A given person (or a given institution) is likely to understand very well one or a few aspects of a risk situation. The given individual may have only fragments of insight on the many other aspects considered in the decision. It follows that careful attention must be given to articulation and communication of the key facts and the rationale for a risk management decision.

This careful attention of course will not necessarily eliminate controversy, but will help to maintain respect for the process and help to channel the criticism of the decision.

U.S. regulatory agencies are more frequently making a risk assessment document available for public information. The promulgation of a final regulation usually includes a preamble outlining the factors considered. The National Academy of Sciences is initiating a study on communication of risk. Although no general review of risk communication is available a few generalizations can be made.

New hazard information should be made generally available as soon as the reasonable scientific integrity of the findings is established. The risk assessment document should place the risk of a carcinogen in understandable perspective. If quantitative expressions of risk are utilized, the range of risks should be clearly shown and if possible a most likely level of risk stated. (8, 14)

Assumptions made in the risk assessment should be clearly stated. (8) Documents resulting from use of decision assisting methodologies should be generally available.

The risk management decision should be accompanied by a listing or discussion of the values considered in making the decision and should reflect the weight given to the more important factors.

The above suggestions for communication are designed to meet the expectations of the highly interested parties. There are of course other sectors of interest (press, other government officials, general academia, etc.). Summarization of the rationale for decisions in concise, yet precise, manner is thus essential. The first objective of the communication process would seem to be preservation and enhancement of the integrity of the decision-making process through openness and candidness. The second objective would be to establish a degree of credibility for the decision on a complex and value-laden issue.

VI. SOME PRINCIPLES FOR RISK MANAGEMENT

In summary, the process leading to risk management decisions on carcinogens can be based upon the same general considerations as one used for reaching decisions on other types of risks. Since the science and the values are more complex than those involved in many other decisions, it seems worthwhile to list a few principles that are particularly relevant to the risk management of carcinogenic agents:

1. Since risk management is driven by risk concerns, significant effort should be directed toward establishing a reasonably complete data base for both hazard assessment and exposure assessment.

2. Because of the lack of complete underlying scientific theory on carcinogenesis, peer review of risk assessment is desirable to bring experienced, multidisciplinary judgment to bear on the presentation of risk information.

3. The operational process of conducting a risk assessment needs to be distinguished from risk management.

4. The legal framework and the traditions of culture will place limits on the degree of discretion in making a risk management decision.

5. Within the limitations of laws and culture, several types of comparative analysis can provide valuable perspective to the risk manager. These include relative risk comparisons, risk/benefit analysis, feasibility analysis, economic/social impact identification, cost and effectiveness analysis (risk/cost/benefit).

6. Laws which provide for a balancing of risk, economic and social impacts provide the greatest flexibility for a technological society.

7. Sound risk management involves significant resources, both in the government sector and on the part of industry -- in developing information, in evaluation and in instituting training, controls, and use limitations. Priorities for research, testing and evaluation are highly important if risk management outputs are to be of greatest benefit.

8. Articulation and communication of the basis for a risk management decision are important in establishing public confidence in the decision process and in the decisions.

Table I

Proportions of Cancer Deaths Attributed to Various Different Factors

Factor or Class of Factors	Percent of all Cancer Deaths: Best Estimate	Percent of all Cancer Deaths: Range of Acceptable Estimates
Tobacco	30	25-40
Alcohol	3	2-4
Diet	35	10-70
Food Additives	1	-5*-2
Reproductive and Sexual Behavior	7	1-13
Occupation	4	2-8
Pollution	2	1-5
Industrial Products	1	1-2
Medicines and Medical Procedures	1	0.5-3
Geophysical Factors	3	2-4
Infections	10?	1-?
Unknown	?	?

* Allowing for a possibly protective effect of antioxidants and other preservatives.

SOURCE: Doll, Richard and Richard Peto. The Causes of Cancer. Oxford University Press, Inc. New York, NY. (1981). p. 1256.

TABLE II

Abbreviated Contents of the OSTP Document - Chemical Carcinogens: Review of the Science and Its Associated Principles (May 1984)

PART I - PRINCIPLES

PART II - STATE OF THE SCIENCE

Chapter 1 - Current Views on the Mechanisms of Carcinogenesis
- Preabsorption Modification of Carcinogens
- Organismic and Cellular Metabolism
- Macromolecular Interactions
- Modification of Altered Genetic Information
- Cancer Formation
- Multiple Agents

Chapter 2 - Short-Term Tests for Potential Carcinogens
- The Short-Term Test Systems
- Factors in Test Evaluation
- Practical Assay Utilization

Chapter 3 - Long-Term Carcinogen Bioassay
- Long-Term Carcinogen Bioassay: Guidelines for Protocols
- Interpretation and Evaluation of Long-Term Evaluation Carcinogen Bioassays
  - Issues of Pathology in the Interpretation of Tumor Data
  - Evaluation of Statistical Significance

Chapter 4 - Current Views on Epidemiological Methods
- Strengths and Limitations of Epidemiology
- Determining Causality
- Epidemiological Studies
- Biochemical Epidemiology
- Implications of Negative Studies

Chapter 5 - Chemical Exposure Assessment
- Methodology of Exposure Assessment
- Broad Issues Affecting Exposure Assessments

Chapter 6 - Utilizing Scientific Data in Assessing Human Cancer Risk Associated With Chemical Exposure
- Steps in the Assessment Process
- Emerging Areas of Science Expected to Impact on Regulatory Actions

TABLE III

Federal Legislative Acts

(Safety, Health and Environment)

Acronym	Common Name	Year Passed
FD&CA	Food, Drug & Cosmetic Act	1938
FIFRA	Federal Insecticide, Fungicide & Rodenticide Act	1947
FHSLA	Federal Hazardous Substances Labeling Act	1960
CAA	Clean Air Act	1963
MVAPCA	Motor Vehicle Air Pollution Control Act	1965
CPTSA	Child Protection & Toy Safety Act	1969
NEPA	National Environmental Policy Act	1970
PPPA	Poison Prevention Packaging Act	1970
OSHA	Occupational Safety & Health Act	1970
NCA	National Cancer Act	1971
CPSA	Consumer Products Safety Act	1972
FWPCA	Federal Water Pollution Control Act	1972
SDWA	Safe Drinking Water Act	1974
HMTA	Hazardous Materials Transportation Act	1975
TSCA	Toxic Substances Control Act	1976
RCRA	Resource Conservation & Recovery Act	1976
CWA	Clean Water Act	1977
CERCLA	"Superfund" (Comprehensive Environmental Response & Liability Act)	1980

TABLE IV

The Matrix of Laws and Regulations Impacting Manufacture and Use of Vinyl Chloride

Law	Agency	Control by Regulation
Occupational Safety and Health Act	OSHA	Workplace exposure limit and prescribed work practices
Clean Air Act	EPA	Limit on air discharge; reports required; limits on residual monomer in PVC
Federal Water Pollution Control Act	EPA	Water Quality Criteria
Federal Insecticide, Fungicide and Rodenticide Act	EPA	Use banned in pesticide formulations
"Superfund"	EPA	Ethylene and chlorine, primary raw materials, subject to tax for cleanup and management of "orphan" hazardous waste sites
Hazardous Materials Transportation Control Act	DOT	Labeling and transportation safety standards
Resources Conservation and Recovery Act	EPA	Disposal of hazardous process wastes subject to standards and reports
Food, Drug and Cosmetic Act	FDA	Packaging films and water pipe subject to de minimis residual monomer; plasticizers and additives subject to approval
Consumer Products Safety Act	CPSC	Use as an aerosol in consumer products banned

TABLE V

Examples of Carcinogenic and Societal Risks

(Probability of Death)

Carcinogenic Risks (Calculated Upper Boundary Risk)[a]		Societal Risks (Statistical Exposure)	
Saccharin (Average Consumption in U.S.)	2.0×10^{-6}(b)	Smoking	3.0×10^{-3}(e)
200 ppm Chloroform in Drinking Water	1.2×10^{-6}(c)	Motor Vehicle Accidents	2.4×10^{-4}(f)
Living Within 5 Miles of a Polyvinyl Chloride Plant	5×10^{-8}(d)	Swimming	3×10^{-5}(g)
		Firefighting	8×10^{-4}(h)

(a) Most probable estimates would be one to two orders of magnitude lower. Source: Hoerger, Fred and John G. Cobler. "Analysis of Agency Estimates of Risk for Carcinogenic Agents." Presented at a meeting of the Society of Risk Analysis. New York, NY. Aug. 2, 1983. (In press: Proceedings of the 2nd Annual Society of Risk Analysis Annual Meeting. 1984)
(b) Wilson, R. and E. Crouch. RISK BENEFIT ANALYSIS. 1982. p. 182.
(c) ibid., p. 187.
(d) Wilson, R. RISKS AND THEIR ACCEPTABILITY. Calculated from data in Table IV.
(e) Wilson, R. RISK BENEFIT ANALYSIS. op. cit.
(f) Ibid., p. 176.
(g) Ibid., p. 180.
(g) Ibid., p. 178.

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TABLE VI

Risks vs. Cost of Exposure Control

Risks to These Factors May Decrease as Exposures are Controlled		Risks to These Factors May Increase as Exposures are Overcontrolled
Environmental	Health	Health and Societal
- Permanent damage	- Death	- Purchasing power
- Reversible effects	- Crippling effects	- Employment
- Aesthetic effects	- Chronic disease	- Security
	- Reversible disease	- Freedom of choice
		- Status/ego
		- Peace of mind
		- Availability of goods
		- Availability of services
		- Convenience
		- Self-esteem
		- Effects of alternatives
		- Nutrition
		- Sanitation

RISK / COST RELATIONSHIP

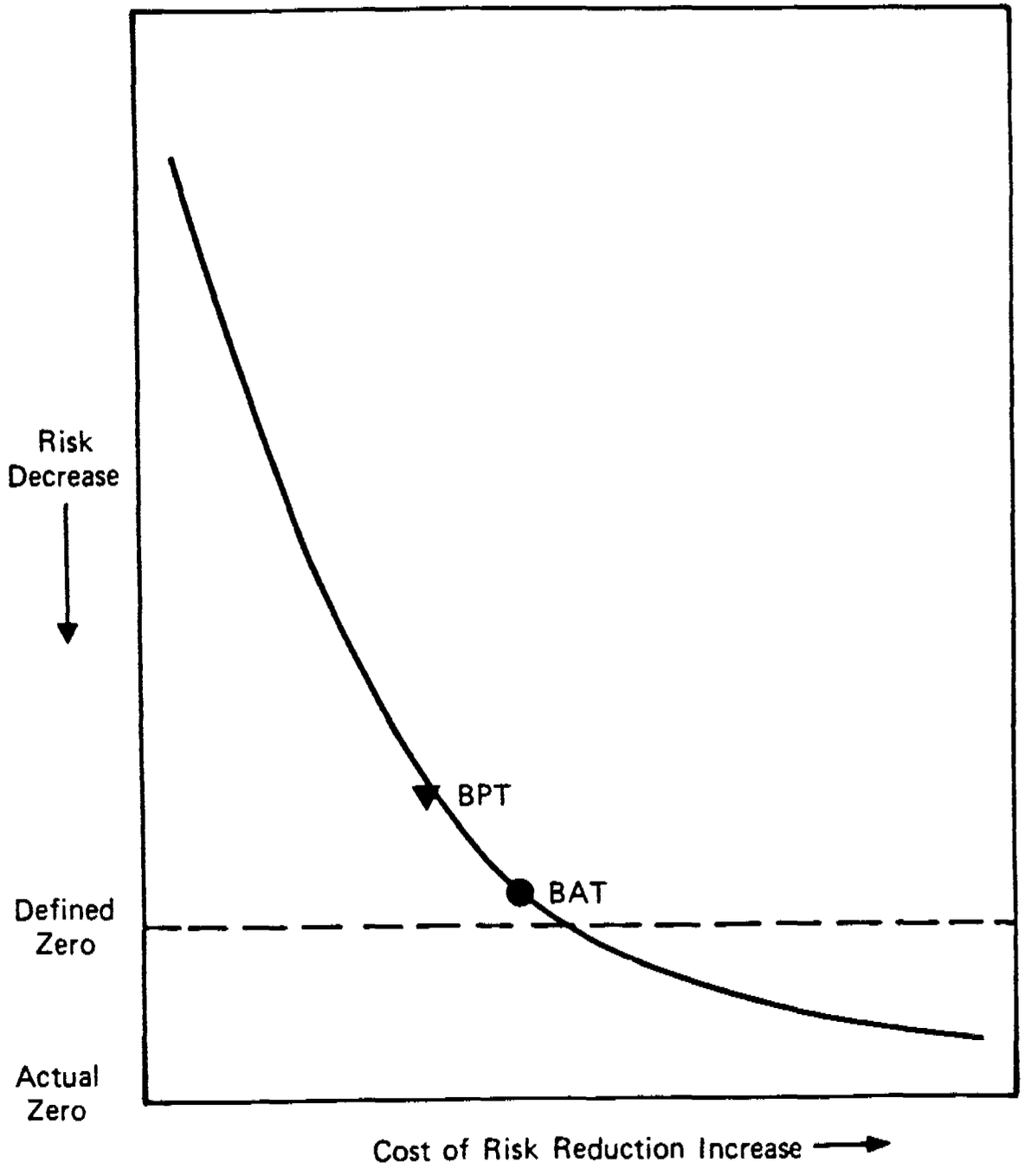

Figure 1

ERRONEOUS PRESUMPTION OF THE RISK / COST / BENEFIT RELATIONSHIP

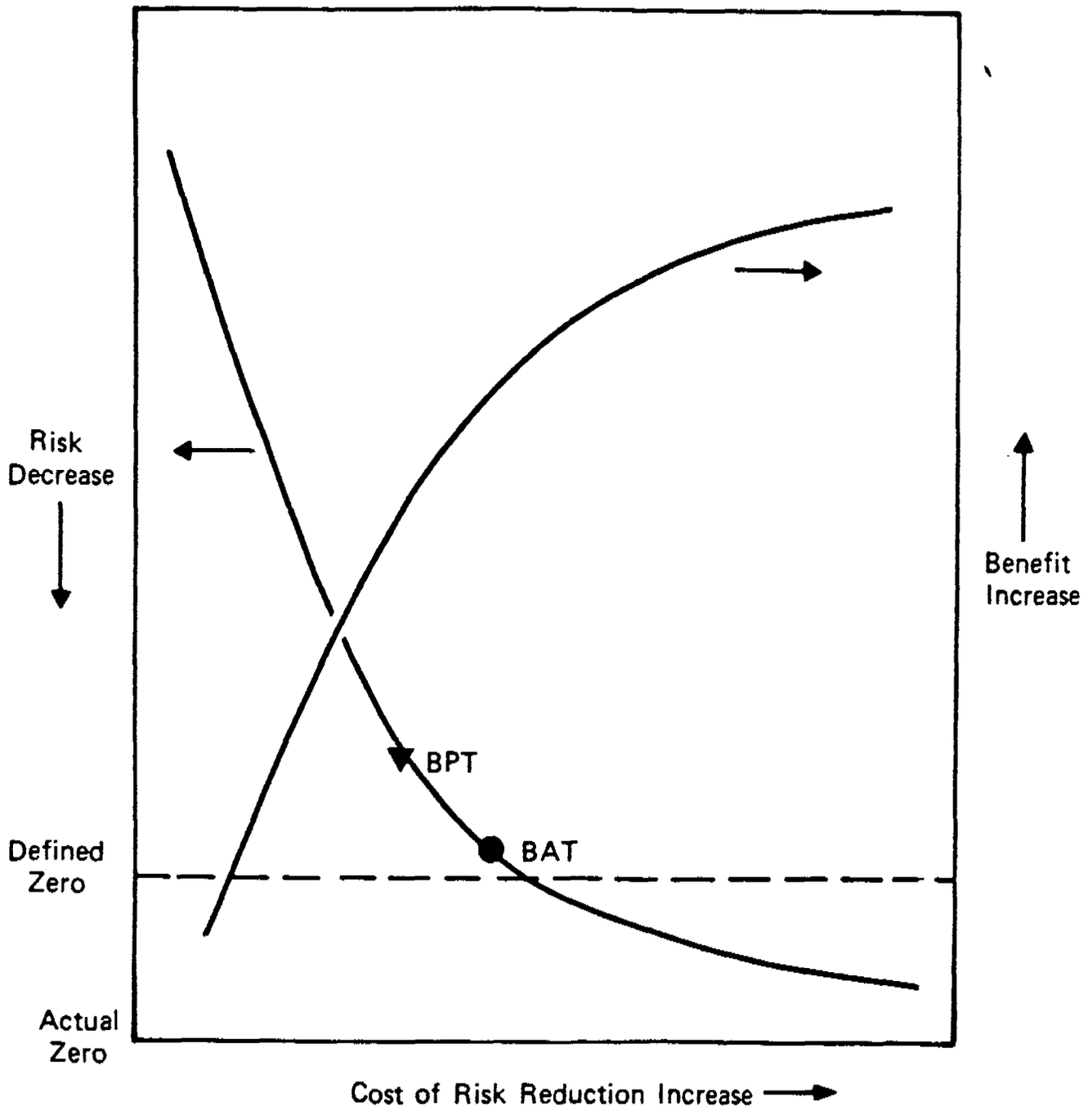

Figure 2

RISK / COST RELATIONSHIP ADJUSTED FOR "NEW RISK" OF CONTROL

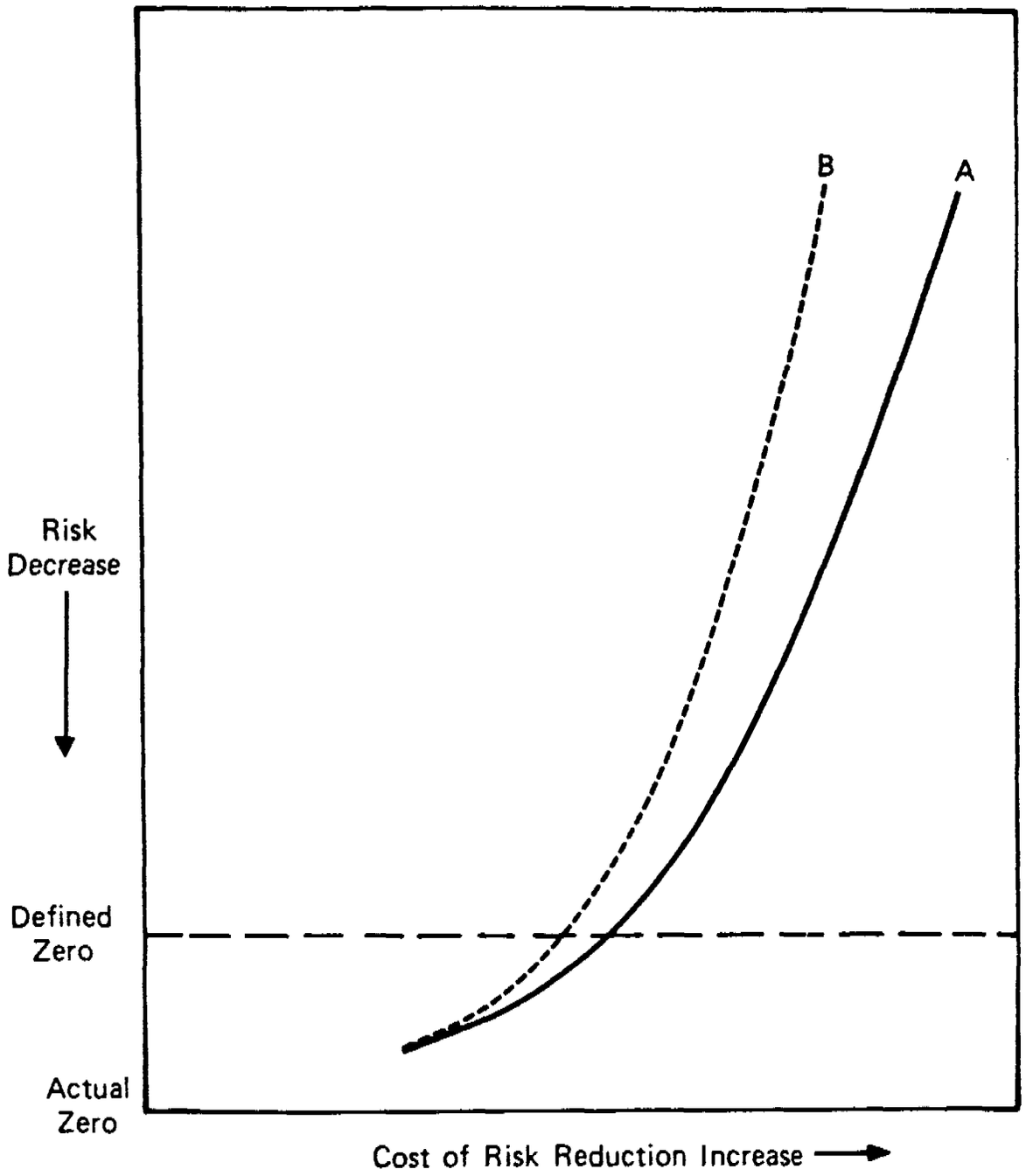

Figure 3

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RISK / COST / BENEFIT RELATIONSHIP

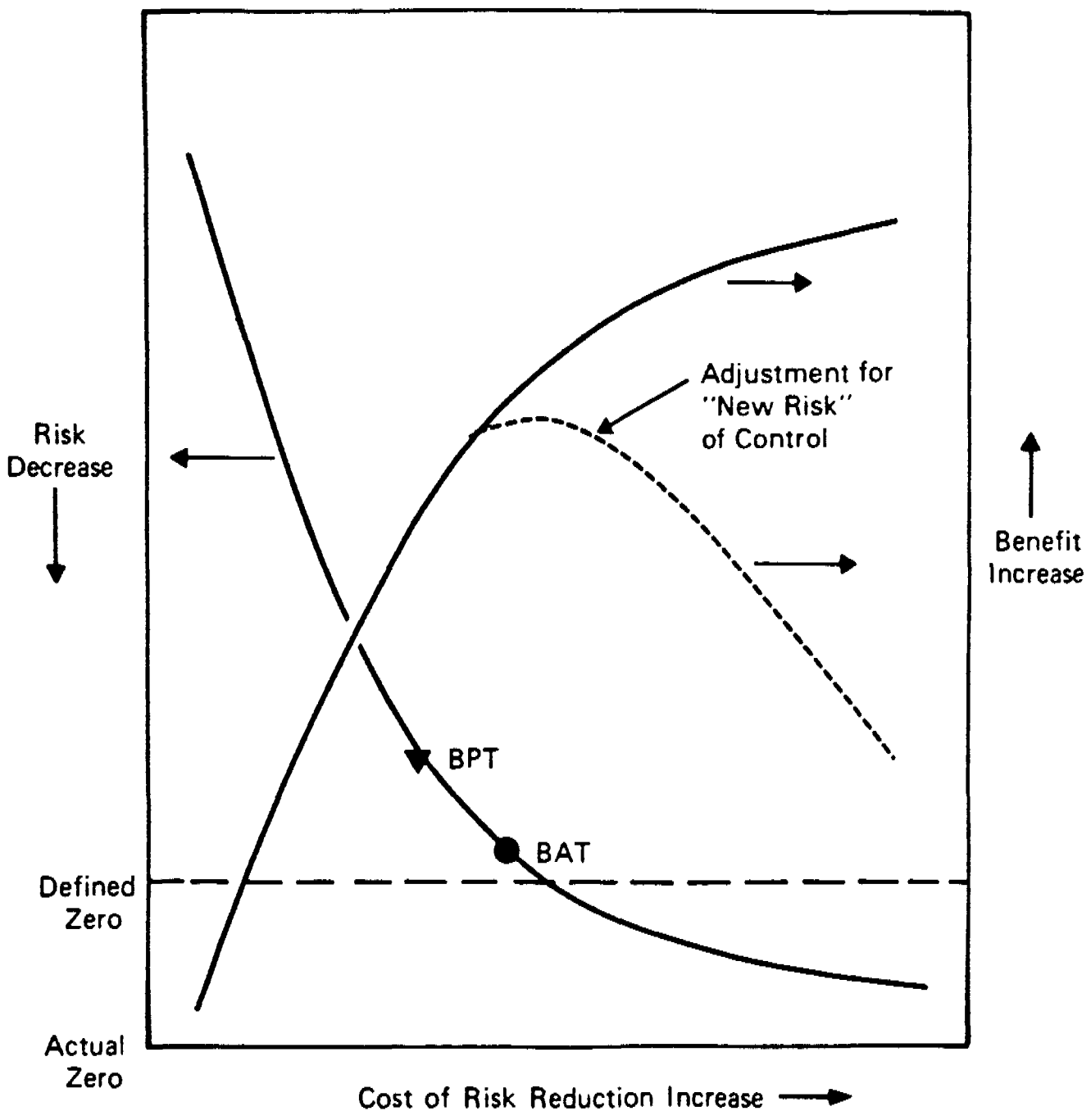

Figure 4

RISK / COST / RISK RELATIONSHIP

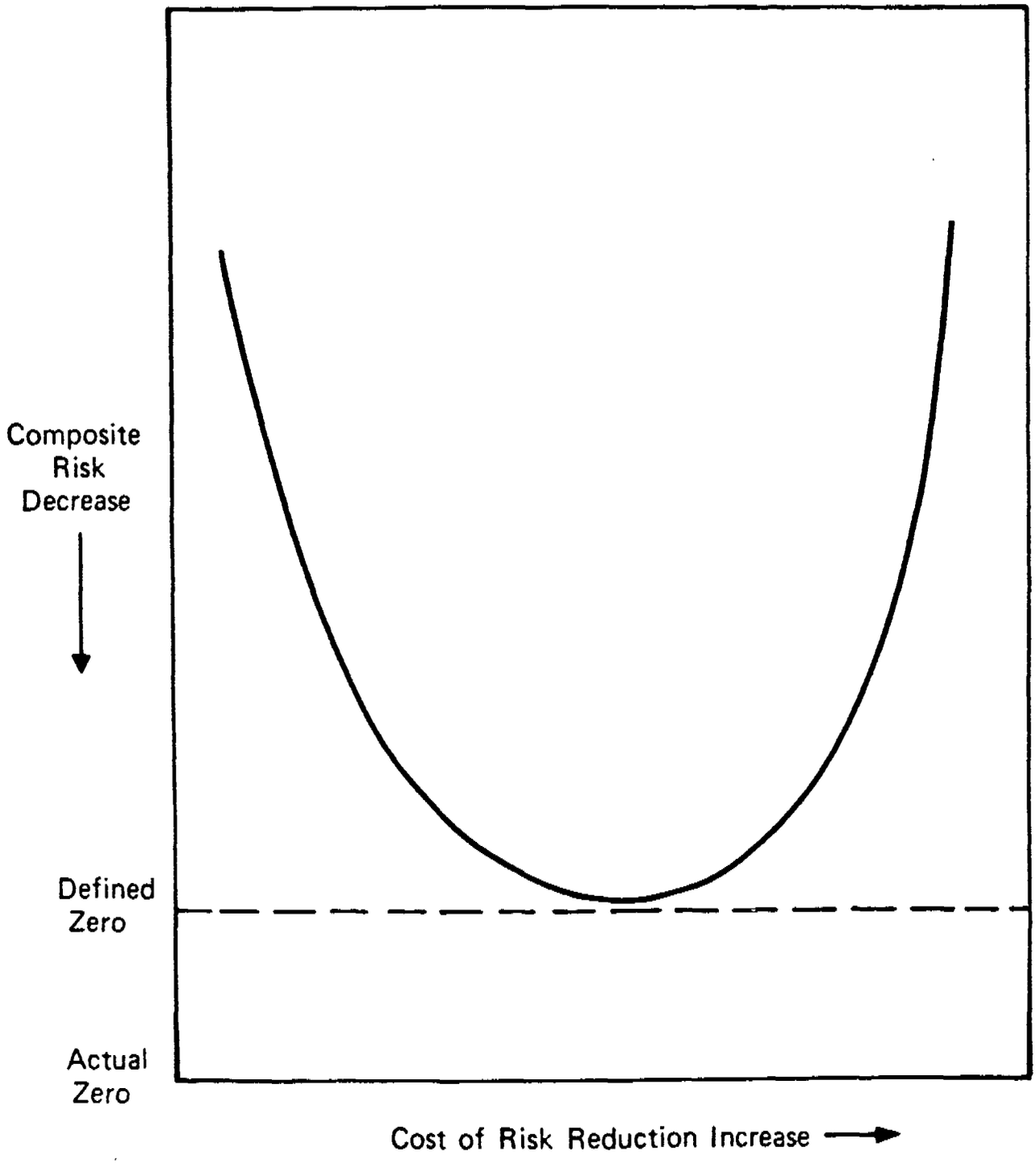

Figure 5

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APPENDIX I

PART I—PRINCIPLES

Preface

The principles contained within this segment of the OSTP carcinogen document were derived by the authors of the various chapters, from the information detailed in Part II, in cooperation with all members of the Interagency Staff Group. This section attempts to provide, in a non-technical form, some important general statements relevant to the evaluation of the role of chemicals in carcinogenesis. These statements are intended to serve as a bridge connecting the basic science as expounded in Part II and the multifaceted process of risk assessment.

Since there are gaps in the information available, differences in evaluations and in scientific opinion may exist about certain of the points highlighted as prinicples. However, these principles derive from a *weltanschauung* utilizing a balanced approach with an appreciation of all elements of the problem, from hazard identification and estimation, through exposure and risk assessment. It is clearly understood that new information and newly emerging concepts may modify some of these statements, however, for the time being, as a result of an ardous cooperative effort these statements, we believe, represent an up-to-date summary on a number of important topics.

I. Principles Derived From the Mechanisms of Carcinogenesis

1. Carcinogenesis is a multistage phenomenon that may involve the genome both directly and indirectly. These stages of carcinogenesis may be, to varying degrees, influenced by a number of variables such as age at exposure, diet, hormonal status, intra- and inter-species variability, which should be considered when trying to predict human response to potentially carcinogenic agents (Chapter 1, Section VI).

2. Appropriate *in vitro* and *in vivo* tests can indicate that an agent has a certain action such as genetic toxicity or promotion. Such information may be useful in evaluating mechanism(s) of cancer induction. However, in evaluation of human risk, the attribution of observed findings of carcinogenicity to a particular biological effect must rest upon sound evidence that the effect is responsible for the cancer induction. It must be kept in mind that a chemical may contribute to carcinogenesis in multuple ways (Chapter 1, Section VI).

3. At the present stage of knowledge, mechanistic considerations, such as DNA repair and other biological responses, in general do not prove the existence of, the lack of existence of, or the location of, a threshold for carcinogenesis. The presence or absence of a threshold for one step of the carcinogenic process does not necessarily determine the presence or absence of a threshold for the whole

process. For example, there is strong evidence that the existence of DNA repair will not result in a threshold for the accumulation of DNA damage (Chapter 1, Section V, Part A); however, the consequences of this for a threshold for carcinogenesis is unclear.

4. The carcinogenic effects of agents may be influenced by non-physiological responses induced in the model systems Testing regimens inducing these responses, such as extensive organ damage, saturation of metabolic pathways, saturation of DNA repair with functional loss of the system, should be evaluated for their relevance to the human response to the agent (Chapter 1, Section V, Part B) and evidence from such a study, whether positive or negative, must be carefully reviewed.

II. Principles for Tests of Cancer Induction

A. Short-Term Tests

5. Short-term tests, such as assays for point mutations, chromosomal aberrations, DNA damage, and *in vitro* transformation are useful in: (1) Screening for potential carcinogens; (2) supporting a judgment on the carcinogenicity of a chemical; and (3) providing information on carcinogenic mechanisms (Chapter 2, Section IV, Part B).

6. At the present, short-term tests are limited in their ability to predict carcinogenicity and cannot supplant data from epidemiological investigations or long-term animal studies since the tests do not necessarily screen for all potential means of cancer induction and do not necessarily mimic all reactions that would occur *in vivo*. Additional research is required to improve existing tests and develop ones that identify chemicals which act by genetic mechanisms not yet detected or which act by other, non-genetic, mechanisms (Chapter 2, Section IV, Part C).

7. Short-term tests should be carefully selected to ensure they have been adequately validated Several tests with different endpoints may be required to characterize a chemical's spectrum of response (Chapter 2, Section IV, Parts A and B).

B. Long-Term Animal Tests

8. In the context of the result from a long-term test, the term carcinogen should be used in a broad sense, *i.e.* a substance or process capable of increasing the incidence of neoplasms (combining benign and malignant when scientifically defensible) or decreasing the time it takes for them to develop. Agents found carcinogenic in animal studies, subject to the considerations discussed in Principles 4 and 14, are considered suspect human carginogens (Chapter 3, Section II, Part A).

9. Some experimental animal models normally have high incidences of certain tumors. The evaluation of tumor data from such animals can pose special problems. For example, the interpretation of cancer incidence in some strains of rats with testicular or mammary tumors, or in some strains of mice with lung or liver tumors must be approached carefully in the light of other biological evidence bearing on potential carcinogenicity (Chapter 3, Section II, Part C).

10. Protocols for long-term tests should be designed to achieve an appropriate balance between the two essential characteristics of a biological assay: Adequate biological and statistical sensitivity (a low false negative rate) and adequate biological and statistical specificity (a low false positive rate) (Chapter 3, Part II, Section D, Number 2). The absence of biases in selection and allocation of animals between control and treatment groups as regards diet, husbandry, necropsy and pathology is crucial (Chapter 3, Part I, Section B, Number 2).

11. It is appropriate to use test doses that generally exceed human exposure levels in order to overcome the inherent insensitivity of the traditional design of the long-term animal test. The highest dose should be selected after an adequate prechronic study and after evaluating other relevant information, *e.g.* pharmacokinetic data, as necessary to determine the highest dose consistent with predicted minimal target organ toxicity and normal lifespan, except as a consequence of the possible induction of cancer (Chapter 3, Section I, Part B, Number 4 and Section II, Part B, Number 1).

12. The diagnosis of pathologic lesions is complicated and requires judgment and appropriate experience. Diagnoses can differ depending on the tissue and species involved and can change with time as techniques improve and data on bioassays accumulate. Accurate interpretation of tumor data is contingent upon careful attention to gross observation, tissue sampling, slide preparation and histologic examination. Diagnosis of tumors should be guided by evidence of their histogenic origin and stage of progression (Chapter 3, Section II, Part C).

13. Appropriate statistical analysis should be performed on data from long-term studies to help determine whether the effects are treatment related or possibly due to chance. These should include a statistical test for trend and a test based on pairwise comparisons including appropriate correction for differences in survival. The weight to be given to the level of statistical significance (the p-value) and to other available pieces of information is a matter of overall scientific judgment (Chapter 3, Section II, Part D).

14. Decisions on the carcinogenicity of chemicals in animals should be based on consideration of relevant biological and biochemical data (Chapter 3, Section II, Part B, Number 3), including the following (Chapter 3, Part II):

(a) Use of background or recent historical control incidence of tissue specific tumors can be an aid in the evaluation of tumor data. Care should be exercised when combining different control groups to avoid inappropriate combinations of such groups.

(b) Evidence of probable reproducibility is important. This evidence can consist of independent confirmation of the original findings or may be derived from intergroup comparisons of tumor incidence data, between dose groups, sexes, strains or species.

(c) Evidence of dose response increases confidence that the effect is treatment related; similarly the lack of an observed dose-response may reduce the likelihood that the effect is associated with the treatment.

(d) Confidence is increased when: (1) The incidence of tumors is markedly elevated in the treated groups compared to controls, particularly when the tumor in controls are infrequent; (2) tumor incidence is significantly increased at multiple anatomical sites; and (3) tumor latency is reduced.

(e) In addition to tumor incidence at specific tumor sites, the stage in the development of neoplasia should be evaluated. For example, the finding that the majority of neoplastic lesions at a specific tissue site is more advanced in a treated group compared to its control may provide additional evidence of a treatment related effect Conversely, the finding that the control group lesions are more advanced might argue that a marginal elevation of tumor incidence is not treatment related.

(f) The incidence of preneoplastic lesions in treatment or control groups may, in certain instances, provide evidence for the biological plausibility of a neoplastic response and contribute to the interpretation of a bioassay.

(g) Identification from prechronic studies, or other toxicity studies of effects in the target organ(s), can assist in evaluating whether or not differences in tumor incidences are treatment related

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(h) Information on the activity of chemicals at the physiological, cellular and molecular level may be important to the evaluation of carcinogenicity data on a case-by-case basis.

III. Principles for Epidemiology

15. The strength of the epidemiological method is that it is the only means of assessing directly the carcinogenic risk of environmental agents in humans; however, because of the limitations of the available information, *e.g.*, the elements discussed in Principle 18 as well as the paucity of data, primary reliance is often placed on animal testing (Chapter 4, Section II, Part A).

16. Descriptive epidemiological studies (based on the measurement of disease rates for various populations), including correlational studies (in which the rate of disease in a population is compared with the spatial or temporal distribution of suspected risk factors), are useful to generate and refine hypotheses, or provide supporting evidence in evaluating relationships detected by other means, but rarely, if ever, provide information allowing a practical causal inference (Chapter 4, Section IV, Part A).

17. Well designed, conducted and evaluated analytic epidemiological investigations of either case-control or cohort variety can provide the basis for practical casual inferences especially useful for public health decisions (Chapter 4, Section IV, Part B).

18. Elements in interpreting the likely practical causality of epidemiological observations include the magnitude of the risk estimates (strength of the associations); the possibility of their being due to chance (statistical significance); the rigor of the study design to avoid various kinds of bias, including those related to selection, confounding, classification and measurement; dose-response relationships; the temporal relationships between exposure and disease; the specificity of the associations; their biological plausibility; and the reproducibility of the findings (Chapter 4, Section III).

19. A high quality negative epidemiological study, while useful, cannot prove the absence of an association between chemical exposure and human cancer. Within the scope of the study, specifically for the populations studied (including concomitant exposures), for the levels and durations of exposure to the agent evaluated and for the time assessed following exposure, likely upper bounds on the estimates of risk can be made and the statistical likelihood of the study to detect an effect can be assessed (Chapter 4, Section VI).

IV. Principles for Exposure Assessment

20. It is desirable that exposure routes employed in animal health effects studies are comparable to human exposure routes both for the simplification of risk assessment and because there may be important route-dependent differences in molecular, biochemical and physical parameters in organs (Chapter 1, Sections II and III).

21. At present, a single generally applicable procedure for a complete exposure assessment does not exist. Therefore, in the near term, it is expected that integrated exposure assessments (utilizing monitoring data, results from physical and chemical models, and consideration of all routes of exposure through all media) will be conducted on a case-by-case basis (Chapter 5, Section II).

22. The depth and accuracy of an exposure assessment should be tailored to provide the degree of knowledge required to support analytical needs. A preliminary assessment using available crude data can often shed light on the upper or lower bounds of potential risks (Chapter 5, Section II, Part D).

23. An exposure assessment should describe the strengths, limitations and uncertainties of the available data and should indicate the assumptions made to derive the exposure estimates (Chapter 5, Section III, Part F).

24. In general, an array or range of exposure values is preferable to a single numerical estimate (Chapter 5, Section III, Part F).

V. Principles for Risk Assessment

25. Decisions on the carcinogenicity of chemicals in humans should be based on considerations of relevant data, whether they are indicative of a positive or negative response and should use sound biological and statistical principles. This weight of evidence approach can include consideration of the following factors and should give appropriate weight to each on a case-by-case basis (Chapter 6, Section II, Part A):

(a) Findings from long-term animal studies (See Principle 14);

(b) Results from epidemiological studies (see Principles 16–18);

(c) *In vivo* and *In vitro* short-term tests;

(d) Structure-activity relationships of chemicals.

(e) Known metabolic differences between animals and humans.

26. No single mathematical procedure is recognized as the most appropriate for low dose extrapolation in carcinogenesis. When relevant biological evidence on mechanism of action (*e.g.*, pharmacokinetics) exists, the models or procedures employed should be consistent with the evidence. However, when data and information are limited, as is the usual case, and when much uncertainty exists regarding the mechanism of carcinogenic action, models or procedures which incoporate low-dose linearity are preferred (Chapter 6, Section II, Part C).

27. The quantification of the various sources of uncertainty involved in cancer risk assessment can be as important as the projection of the risk estimate itself. The sources that might be addressed include:

(a) The statistical uncertainty associated with the given risk estimate;

(b) The variability introduced by the selection of a particular low-dose extrapolation procedure;

(c) When risk estimation is based on laboratory generated data, the biological variability associated with the use of a particular test organism and its scaling or extrapolation to man (Chapter 6, Section II, Part D).

28. An estimate of cancer risk for humans exposed to an agent can be no more accurate than an exposure assessment that it utilizes. Lack of adequate exposure data is frequently a major limiting factor in evaluation of carcinogenic risks for humans (chapter 6, Section II, Part B).

29. While several considerations often enter the risk assessment process, it is important to try to maintain a clear distinction among facts (statements supported by data), consensus (statements generally held in the scientific community), assumptions (statements made to fill data gaps), and science policy decisions (statements made to resolve points of current controversy) (Chapter 6, Section II, Part D).

30. Differences in human susceptibility, and variable and extreme exposures to chemicals suggest the likelihood that there are subpopulations that are at greater than average risk. (Chapter 1, Section III, Part C, and Chapter 5, Section II, Part C). Increased consideration should be given to the identification of high risk populations.

31. Because of the uncertainties associated with risk assessment, a full evaluation of risk to humans should include a qualitative consideration of the basic strengths and weaknesses of the available hazard and exposure data in addition to any numerical estimations that are made (Chapter 6, Section II, Part D).

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