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Health Risk Assessment of Environmental Agents: Incorporation of Emerging Scientific Information

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I. Introduction

The objective of the U.S. Environmental Protection Agency's (EPA) risk assessments are to support environmental decision making. Assessments of risks to environmental agents serve not only the regulatory programs of the EPA but also State and local agencies, as well as international communities that are addressing environmental issues. The ingredients of health risk assessment include information on whether a chemical produces adverse health effects, how the frequency of adverse effects changes with dose, and to what degree and under what conditions people may be exposed as pollutants travel in the environment. The primary sources of information for judging human risk are human epidemiologic and animal toxicological studies, and other empirical information such as genotoxicity, structure–activity relationship, and exposure data. Risk assessments rely on studies in animals because human data are not usually available. The health-related information available on agents is typically incomplete. Moreover, health risk assessments on environmental agents must usually address the potential for harm from exposure levels found in the environment that are usually lower than concentrations at which toxicity is found in laboratory animal or epidemiologic studies. Thus, the extrapolations that are required to project human risk (i.e., from high to low doses, from nonhuman species to human beings, from one route to another route of exposure) inherently introduce uncertainty.

Given that extrapolations must be performed, risk assessment is complex and often controversial. EPA develops risk assessment guidelines to provide staff and decision

makers with guidance and perspectives necessary to develop and use effective health risk assessments. Guidelines also encourage consistency in procedures to support decision making across the many EPA programs. The following lists the risk assessment guidelines that EPA has published:

- Carcinogenicity (1)(2)
- Mutagenicity (3)
- Developmental toxicity (4)
- Reproductive toxicity (5)
- Neurotoxicity (6)
- Exposure (7)
- Complex mixtures (8).

EPA recently proposed new cancer risk assessment guidelines to bring current and relevant science into future assessments and to promote research that applies new knowledge to specific pollutants. There have been significant gains in our understanding of the cellular and subcellular processes that result in cancer, and these advances have enabled research on the ways environmental contaminants act on cells to cause cancer. These new guidelines will be discussed throughout this article as an illustration of how new science is impacting and improving the characterization of potential human risk.

Health risk assessment practices are evolving on a number of fronts (see Table 1). Risk analyses have historically relied to a large degree on observations of frank toxic effects (e.g., tumors, malformations). Risk assessments are moving from this

phenomenologic approach by identifying the ways environmental agents are changed though metabolic processes, the dose at the affected organ system, and how an agent produces its adverse effects at high doses and at low ones. This understanding of how an agent produces its toxic effect is beginning to break down the dichotomy that has existed between assessments of cancer and noncancer risks. Of equal importance, the "one-size-fits-all" approach is being replaced by emphasizing the ascertainment of risk to susceptible subpopulations. EPA recently put forth a new national agenda to protect children from toxic agents in the environment (9). In addition, to make risk assessments more understandable and useful, there is an increased emphasis on risk characterization. Risk characterization is the final output of the risk assessment process from which all preceding analyses (i.e., from the hazard, dose–response, and exposure assessments) are tied together to convey in nontechnical terms the overall conclusions about potential human risk, as well as the rationale, strengths, and limitations of the conclusions.

This article discusses several trends occurring in risk assessment in the context of the risk paradigm—hazard, dose–response, and exposure assessments and subsequent risk characterization (see Figure 1). Chemical examples are provided to illustrate these emerging directions in health risk assessment.

II. Evolution of Hazard Assessment

In its 1994 report about the use of science and judgment in risk assessment, the National Research Council of the National Academy of Science recommended that EPA

incorporate technical characterizations of risk that are both qualitative and quantitative in its assessments (10). Thus, hazard identification as well as dose–response and exposure analyses are changing by the increased emphasis on providing characterization discussions. These technical characterizations essentially reveal the thought process that leads to the scientific judgments of potential human risk. The technical hazard characterization explains the extent and weight of evidence, major points of interpretation and rationale, strengths and weaknesses of the evidence, and discusses alternative conclusions and uncertainties that deserve serious consideration. The technical hazard characterization along with those for the dose–response and exposure assessments are the starting materials for the risk characterization process (see Section V) that completes the risk assessment. As shown in Figure 2, this concept of technical hazard characterizations has been incorporated into EPA's revised *Guidelines for Carcinogen Risk Assessment* (2).

A. Expanding Role of Mechanistic Data

Hazard assessment is moving beyond relying on traditional toxicology by using a weight-of-evidence (WoE) approach that considers all relevant data and the mode of action of the given agent. It is the sum of the biology of the organism and the chemical properties of an agent that leads to an adverse effect. Thus, it is an evaluation of the entire range of data (e.g., physical, chemical, biological, toxicological, clinical, and epidemiological information) that allows one to arrive at a reasoned judgment of an agent's potential to cause human harm. For example, EPA has proposed a major change in

the way hazard evidence is weighed in reaching conclusions about the human carcinogenic potential of environmental agents (2)(11). Rather than relying heavily on tumor findings, the full use of all relevant information is promoted and an understanding of how the agent induces tumors is emphasized. Under the proposed revisions to EPA's 1986 *Guidelines for Carcinogen Risk Assessment* (1), a short WoE narrative is derived from the longer technical hazard characterization. The WoE narrative is intended for risk managers and other users, and it replaces the current six alphanumeric classification categories; A, human carcinogen; B1/B2, probable human carcinogen; C, possible human carcinogen; D, not classifiable, and E, evidence of noncarcinogenicity. This narrative explains in nontechnical language the key data and conclusions, as well as the conditions for hazard expression. Conclusions about potential human carcinogenicity are presented by route of exposure. Contained within this narrative are simple likelihood descriptors that essentially distinguish whether there is enough evidence to make a projection about human hazard (i.e., known human carcinogen, should be treated as if known, likely to be a human carcinogen, or not likely to be a human carcinogen) or whether there is insufficient evidence to make a projection (i.e., the cancer potential cannot be determined because evidence is lacking, conflicting, inadequate, or because there is some evidence but it is not sufficient to make a projection to humans). Because one encounters a variety of data sets on agents, these descriptors are not meant to stand alone; rather, the context of the WoE narrative is intended to provide a transparent explanation of the biological evidence and how the conclusions were derived. Moreover, these descriptors should not be viewed as

classification categories (like the alphameric system), which often obscure key scientific differences among chemicals. The new WoE narrative also presents conclusions about how the agent induces tumors and the relevance of the mode of action to humans, and recommends a dose–response approach based on the mode-of-action understanding (see Section III.B). Some examples of how mechanistic information on chemicals has informed risk assessments or provided a better basis for interpreting the meaning of effects from animal data and its relevance to humans are given in the following subsections.

1. $\alpha_{2\mu}$ Nephropathy and Kidney Cancer

The development of male rat kidney tumors mediated by $\alpha_{2\mu}$-globulin is one of the more thoroughly studied processes in cancer toxicology. Exposure to several agents, such as 2,2,4-trimethylpentane (and unleaded gasoline) and *d*-limonene, have been reported to result in an accumulation of protein droplets containing $\alpha_{2\mu}$-globulin in the epithelial cells of the proximal convoluted tubules of male rat kidneys (12)(13)(14)(15). This protein accumulation is thought to result in renal cell injury and proliferation, and eventually renal tubule tumors. Female rats and other laboratory animals do not accumulate this protein in the kidney and, when exposed to alpha$_{2u}$-globulin inducers, do not develop an increased incidence of renal tubule tumors. The manner in which the human male responds to such agents is uncertain. This mechanism appears to be specific to the rat given the results from studies of other laboratory species, and given the high doses that are needed to produce an effect in the male rat.

In 1991, EPA concluded that the sequence of events proposed to link $\alpha_{2\mu}$-globulin accumulation to nephropathy and renal tubule tumors in the male rat is plausible, although not totally proven; that the $\alpha_{2\mu}$-globulin response following chemical administration appears to be unique to the male rat; and that the male rat kidney response to chemicals that induce $\alpha_{2\mu}$-globulin is probably not relevant to humans for purposes of risk assessment (15). However, when chemically induced $\alpha_{2\mu}$-globulin kidney tumors are present, other tumors in the male rat and any tumor in other exposed laboratory animals may be important in evaluating the carcinogenic potential of a given chemical. Some investigators think that the issue of $\alpha_{2\mu}$ nephropathy and kidney cancer is not resolved and have proposed alternative hypothesis (16). Should significant new information on $\alpha_{2\mu}$-globulin kidney tumors become available, EPA will update its policy position accordingly.

2. Perturbation of Pituitary–Thyroid Homeostasis and Thyroid Cancer

The ways in which antithyroid compounds induce thyroid tumors are also reasonably well understood, even though the precise molecular events leading to thyroid follicular cell tumors are not totally described. Experimental findings in rodents have shown that perturbation of hypothalamus–pituitary–thyroid homeostasis leads to elevated thyroid-stimulating hormone (TSH) levels, which in turn results in increased DNA synthesis and cell proliferation, and eventually to thyroid gland tumors (17)(18)(19)(20). Thus, thyroid tumors are secondary to a hormone imbalance. Agents with antithyroid activity include sulfamethazine and other thionamides. There is uncertainty whether prolonged stimulation

of the human thyroid by TSH may lead to cancer. Because this possibility cannot be dismissed, it is presumed that chemicals that produce thyroid tumors in rodents may pose a carcinogenic risk to humans. Humans (including other primates) are thought to be substantially less sensitive than rats to this mechanism.

One factor that may account for the interspecific difference in sensitivity concerns the influence of protein carriers of thyroid hormones in the blood. Rodent thyroid hormones are more susceptible to removal from the body because of the lack of a high-affinity binding protein, which humans possess (21). In the rat, there is chronic stimulation of the thyroid gland by TSH to compensate for the increase turnover of thyroid hormones. This may render the rat more sensitive to disturbances in TSH levels. EPA has recently proposed science policy guidance on the consideration of thyroid carcinogenesis in risk assessment(20). Briefly, it is proposed that chemicals that produce rodent thyroid tumors should be presumed to pose a hazard to humans; evaluations of human thyroid cancer risk from long-term perturbations of pituitary–thyroid function in rodents should incorporate considerations about potential interspecific differences in sensitivity and evaluate the applicability of potential human exposure patterns in relation to the findings in animal models. Dose–response approaches should be based on mode-of-action information; application of nonlinear approaches are appropriate for those nonmutagenic chemicals shown to cause a hormonal imbalance. However, those antithyroid compounds with mutagenic activity need to be carefully evaluated on a case-by-case basis.

3. Bladder Calculi and Tumors

Another situation for which the rat appears to be quantitatively more sensitive than humans is the induction of bladder tumors secondary to bladder calculi–induced hyperplasia. Cohen and Ellwein (22) reported that if the administered dose of a chemical (e.g., for melamine, uracil, calcium oxalate, orotic acid, glycine) is below the level that causes calculus formation, there is no increase in cell proliferation; consequently, there is no increase in bladder tumors. Thus, calculus-forming compounds would have a threshold of response. EPA has considered this in its assessment of melamine (23).

4. Formaldehyde and Nasal Tumors

The understanding of formaldehyde carcinogenicity has developed over a number of years since Kerns et. al. (24) demonstrated that inhalation exposure to formaldehyde caused nasal squamous cell carcinomas in mice and rats. In 1991, the carcinogenicity of formaldehyde was reassessed using data from rats and monkeys: Levels of DNA protein cross-links (DPX) were evaluated with a linearized multistage (LMS) model (25). Using DPX as a more precise measure of dose resulted in risk estimates that were significantly lower than those derived by using external exposure only. Although the mechanisms of formaldehyde carcinogenesis are not completely understood, data have continued to provide additional insight into the cancer risk associated with low-dose exposure to inhaled formaldehyde by defining more precisely the location of the nasal tumors in the rat, determining rates of cell proliferation in the nose, and establishing the delivered dose (i.e.,

levels of DPX) to the target tissue as well as rates of repair of DPXs after repeated exposures (26)(27)(28)(29). Precursor response data also may have implications in the estimation of risk to humans. In the rat, the dose–response relationships of induction of nasal tumors and of cell proliferation correspond and are both highly nonlinear (28). DPXs do not accumulate; and although the dose–response relationship is linear in the range of tumor induction and increase cell replication, the slope is greater than at lower dose ranges due to saturation of detoxification (26). Although formaldehyde is a mutagenic carcinogen, the data on tumors, cellular kinetics, and molecular dosimetry indicate that the dose–response relationship is not linear throughout the entire range, but is subject to an upward curvature due to increased cell proliferation.

B. Conditions of Hazard Expression

As mentioned earlier, hazard assessment has expanded from simply identifying adverse effects to fuller technical characterizations of a particular hazard. One dimension critical to characterizing hazard potential is the concept of hazard expression (i.e., What are the circumstances under which a particular hazard is expressed?). For example, an agent may not carry the same hazard potential for different routes of exposure. Inhalation exposure to vinyl acetate (600 parts per million) produces statistically significant increases in nasal tumors in rats, where as no statistically significant increases in tumors are observed when the compound is ingested orally via drinking water (30)(31). Likewise, a compound's carcinogenicity may be dose limited. Although methylmercury has been

shown to produce tumors in mice at high doses (32), it is unlikely to pose a hazard to humans at low doses. Conditions of hazard expression may not only involve exposure conditions (e.g., route, magnitude, or duration) but may depend on biological and physiological processes.

Studies on metabolism may provide pertinent data about the circumstances that affect hazard expression. The biotransformation of many chemicals to reactive compounds is dependent on the presence of certain metabolic pathways (e.g., oxidative pathways involving P_{450} cytochromes or conjugation pathways involving glutathione S-transferases). For example, 1,3-butadiene is carcinogenic in rats and mice, with mice being more sensitive to tumor induction than rats (33)(34). It is thought that the carcinogenic potential of 1,3-butadiene is dependent on metabolic activation to reactive metabolites, which interact with DNA. For example, metabolism of 1,3-butadiene to reactive epoxides is substantially greater in mice than in rats (35)(36)(37). Although it has been reported that humans exposed to 1,3-butadiene show a higher incidence of chronic leukemia (38), the available metabolic studies suggest that humans may not be as highly susceptible as mice. Thus, metabolizing enzymes can account for different susceptibilities among species. Other biological factors that can result in differences in sensitivity include age, sex, or preexisting diseases. These factors that may contribute to special sensitivity to a given agent as discussed further in the following section.

C. Variation in Human Susceptibility

Certain individuals may be at an increased risk because their activity patterns increase their exposure or because their proximity to a source means higher exposures to environmental contaminants. Humans also may vary in their susceptibility to toxicity because of preexisting disease conditions or differences in age, gender, metabolism, or genetic makeup. For example, a number of studies have shown the role of carcinogen-metabolizing enzyme polymorphisms in cancer susceptibility (reviewed in Ref. (39)), of which the most convincing is for the association of the GSTM1 homozygous genotype and the CYP1A1 rare alleles with lung cancer in Japanese (40)(41). Gene–environmental interactions have also been shown to be important to an elevated risk for developmental defects. For example, genetic variation of transforming growth factor-alpha and maternal smoking have been associated with increased risk for delivering infants with cleft lip or palate (42)(43). Human responses may vary due to environmental exposures during different periods of the life cycle. Exposures of the fetus or neonate may disrupt developing systems, thereby resulting in increased sensitivity. EPA has consider in its risk assessments subgroups with a high sensitivity to environmental pollutants, as evinced by the National Ambient Air Quality Standards for air pollutants and lead. Two examples are discussed in the following subsections.

1. Methylmercury and Neurobehavorial Effects in Children

Mercury is ubiquitous and persistent in the environment. It occurs in both natural (e.g., volcanoes, soils, wildfires) and industrial (e.g, coal combustion, mining, waste incineration) sources. A form of mercury that is particularly hazardous to humans is methylmercury. A primary pathway of human exposure is by consuming fish that have accumulated methylmercury. Microorganisms in the sediment of the earth's waters can convert mercury into methylmercury. It is well established that methylmercury is a neurotoxin (44). The developing nervous system of the fetus is especially sensitive to the effects of methylmercury. Animal and human studies indicate that in utero exposure to methylmercury can potentially result in adverse neurobehavioral effects on children.

To protect sensitive subpopulations (e.g., infants exposed pre- and postnatally), in 1995 EPA established a reference dose (i.e., a quantitative estimate of levels expected to be without effects) of 1×10^{-4} mg/kg/day based on available human studies in Iraq (45). This study was based on 81 infant–mother pairs that had consumed seed grain that had been fumigated with methylmercury. The results of two recent epidemiologic studies of fish-eating populations—one in the Seychelles Islands and the other in the Faeroe Islands—are anticipated to shed further light on the dose–response issues associated with the oral intake of methylmercury intake via contaminated food. It should be noted, like exposure to lead, the neurological effects associated with low exposures to methylmercury may be subtle and delayed, thus making it difficult to identify in young children. Lead is one of the best studied examples of prenatal exposure and it subsequent affects on cognitive and behavioral development of young children (46). EPA as well as other

Federal agencies have published strategy documents in an effort to reduce children's exposure to lead (47)(48)(49).

2. Air Pollution and Respiratory Effects in the Elderly and Children

The elderly (65 years and older) make up another population susceptible to environmental pollution. For example, several morbidity (e.g., hospital admissions) and mortality studies provide evidence that the elderly (especially those with underlying respiratory or cardiac diseases) are more susceptible to the short- and long-term effects of particulate air pollution than are young healthy adults (50)(51)(52)(53). Particulate air pollution might aggravate the severity of preexisting chronic respiratory or cardiac diseases. Approximately 40% of people over 75 years old have some form of heart disease, 35% have hypertension, and 10% have chronic obstructive pulmonary disease (e.g., asthma) (53). Also, the elderly have had more cumulative exposure over their life span and hence more opportunity to accumulate particles or damage in their lungs. Although there is an association of short-term, low-level ambient exposure to particulate matter and excess mortality or morbidity among the elderly, the biological plausibility of these findings remains unclear. The few studies available also suggest that children, particularly those with preexisting respiratory diseases, may be potentially more susceptible than the general population to the pulmonary effects of air pollution (53)(54).

D. Integrative Analysis of Cancer and Noncancer Health Effects

In evaluating health risks posed by environmental agents, EPA considers both cancer and noncancer effects. Some of the noncancer effects specifically considered are developmental and reproductive toxicity, neurotoxicity, immunotoxicity, and respiratory toxicity, as well as systemic organ toxicities. Historically, assessments have been done separately and very differently for cancer and noncancer health effects. An important direction in assessments of environmental agents is to provide more integrated characterizations of cancer and noncancer health effects. The dichotomy between cancer and noncancer is beginning to break down with a better understanding of the mechanisms of toxicity. Also, the quantitative approaches are merging as discussed in Section III. The underlying basis for certain noncancer toxicities and cancer may have several commonalties. For example, chemically induced toxicity can cause cell death. Surviving cells may then compensate for that injury by increasing cell proliferation (hyperplasia), which may underlie many types of toxic responses. If this proliferative activity continues unchecked, it may result in tumors. Chemicals may modulate or alter gene expression via receptor interactions. Thus, receptor-mediated pathways may play a role in both carcinogenesis and other organ system toxicities. For example, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and dioxin-like compounds bind to the A*h* receptor, which may represent the first step in a series of events leading to cellular and tissue changes in normal biological processes. Thus, dioxin (and dioxin-like compounds) may exert its

carcinogenic, immunologic, and reproductive effects via A*h* receptor–dependent events (55)(56)(57).

EPA is attempting to integrate combined human health and ecological risk assessments to ensure that decision makers at all levels have an integrated view of risk, which is essential to making sound decisions. Human health and ecological assessments make use of similar data. For example, studies of piscivorous birds that have consumed methylmercury-contaminated fish show neurobehavioral effects similar to those of exposed human beings (58)(59). A recent concern has been raised in the news (e.g., *Esquire* and *The New Yorker*, January 1996) and among scientists about the accumulation in the environment of chemicals (e.g., pesticides like DDT/DDE and kepone, certain polychlorinated biphenyls) that may mimic natural sex hormones. There have been several reports suggesting that a decline in sperm number in human males over the last 50 years (60), as well as effects on male reproduction in wildlife species (e.g., male alligators exposed to pesticides in Florida's Lake Apolka with reduced genitalia). For example, DDE (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane)—which was shown to cause reproductive failure (due to eggshell thinning) in birds over two decades ago—has been shown to inhibit androgen binding to the androgen receptor, which may account for its account for its ability to alter male reproductive development (61). Because wildlife species and domestic animals share the same environment with humans and are in the human food web, these nonhuman species serve as sentinels for potential human health risks posed by environmental contaminants (for review see Ref.(62)).

III. Trends in Dose-Response Assessment

Historically, dose-response assessment has been done very differently for cancer and noncancer health effects. For nearly two decades, EPA has modeled tumor risk by a default approach based on the assumption of low-dose linearity. To estimate human cancer risk, the LMS model was applied, which extrapolates risk as the 95% upper-bound confidence interval (1)(63)(64). The standard practice for noncancer health assessment has assumed the existence of a threshold for adverse effects. Acceptable exposures for chemicals causing noncancer effects have been estimated by applying uncertainty factors (UFs) to a determined *no-observed-adverse-effect level* (NOAEL), which is the highest dose at which no adverse effects have been detected. If a NOAEL cannot be established, then a *lowest-observed-adverse-effect level* (LOAEL) is determined for the critical effect. The UFs may be as much as 10 each and are intended to account for limitations in the available data, such as human variation, interspecific differences, lack of chronic data, or lack of certain other critical data. In the reference concentration (RfC) method, the composite UF for interspecific differences is 3 because of dosimetric adjustments (65)(66). The NOAEL (or LOAEL) is divided byUFs o establish a reference dose (RfD) for oral exposures or an RfC for inhalation exposures, which is an estimate (with uncertainty spanning perhaps an order of magnitude) of daily exposure (RfD) and continuous exposure (RfC) that is likely to be without an appreciable risk of deleterious effects during a lifetime (66)(65)(67)(68)(69). RfDs and RfCs are not derived using composite UFs

greater than 10,000 and 3,000, respectively. The NOAEL can be compared with the human exposure estimate to derive a margin of exposure.

A. Modeling in the Range of Observation for Both Cancer and Noncancer Risks

With recent proposals to model response data in the observable range to derive points of departure[1] both for cancer and noncancer endpoints (2)(44), EPA health risk assessment practices are beginning to come together. The modeling of observed response data to identify points of departure in a standard way will help to harmonized cancer and noncancer dose–response approaches and permit comparisons of cancer and noncancer risk estimates.

1. Benchmark Dose Approach: Noncancer Assessment

The traditional NOAEL approach for noncancer risk assessment has often been a source of controversy and has been criticized in several ways. For example, experiments involving fewer animals tend to produce larger NOAELs and, as a consequence, may produce larger RfDs or RfCs. The reverse would seem more appropriate in a regulatory context because larger experiments should provide greater evidence of safety. The focus of the NOAEL approach is only on the dose that is the NOAEL, and the NOAEL must be one of the experimental doses. Moreover, it also ignores the shape of the dose–response

[1]Point of departure is conceptually similar to benchmark dose, which has been used for noncancer assessment.

curve. Thus, the slope of the dose response plays little role in determining acceptable exposures for human beings. These and other limitations prompted development of the alternative approach of applying uncertainty factors to a benchmark dose (BMD) rather than to a NOAEL (70). Essentially, the BMD approach fully uses all of the experimental data to fit one or more dose-response curves for critical effects that are, in turn, used to estimate a BMD that is typically not far below the range of the observed data. The BMD approach allows for a more objective approach in developing allowable human exposures across different study designs encountered in noncancer risk assessment.

The BMD is defined as a statistical lower confidence limit (CL) on the dose producing a predetermined level of change in adverse response (BMR) compared with the response in untreated animals (70). The choice of the BMR is critical. For quantal endpoints, a particular level of response is chosen (1%, 5%, or 10%). For continuous endpoints, the BMR is the degree of change from controls and is based on what is considered a biologically significant change. The methods of CL calculation and choice of CL (90%, 95%) are also critical. The choice of extra risk versus additional risk is based to some extent on assumptions about whether an agent is adding to the background risk. Extra risk is viewed as the default because it is more conservative. Several RfCs and an RfD based on the BMD approach are included in the EPA's Integrated Risk Information System (IRIS) Database.[2] These include methylmercury based on delayed postnatal

[2]IRIS can be accessed via the Internet at http://www.epa.gov/ngispgm3/IRIS/index.html, or call (513) 569-7254 for more information.

development in humans, carbon disulfide based on neurotoxicity, 1,1,1,2-tetrafluoroethane based on testicular effects in rats, and antimony trioxide based on chronic pulmonary interstitial inflammation in female rats. It should be noted that the BMD approach is still under discussion and development. The BMD approach is further discussed in Refs. (70), (71), (72), (73).

2. Two-Step Process for Cancer Dose-Response Assessment

EPA recently proposed to replace its method for extrapolating low-dose cancer risk by applying the LMS procedure. Instead, it would apply a two-step process that distinguishes between what is known (i.e., the observed range of data) and what is not known (i.e., the range of extrapolation) (2)(11). Thus, the first step involves modeling response data in the empirical range of observation (Figure 3). The proposed guidelines indicate a preference for modeling with a biologically based (74) or case-specific model. Because the parameters of these models require extensive data, it is anticipated that the necessary data to support these models will not be available for most chemicals and that modeling in the observed range will probably be done most often with an empirical curve-fitting approach. A point of departure is determined from this modeling. A standard point of departure was proposed (and which is subject to public comment) as the lower 95% CL on a dose associated with 10% extra risk (LED_{10}). Other points of departure may be appropriate (e.g., if a response is observed below an increase in response at 10%). The objective is to determine the lowest reliable part of the dose–response curve for the

beginning the second step of the process—the extrapolation range (discussed in the next section). For some data sets (e.g., certain continuous data), estimating an LOAEL or NOAEL may be more suitable than determining a point of departure.

B. The Range of Extrapolation for Cancer Risk

The second step involves extrapolation below the range of observation. As mentioned earlier, a biologically based or case-specific model is preferred for extrapolating low-dose risk. If the available data do not permit such approaches, the proposed guidelines provide for several default extrapolation approaches (linear, nonlinear, or both), which begin with the point of departure. The extrapolation default approach that is taken should be based on the mode-of-action understanding about the agent. As discussed earlier, the understanding of the underlying biological mechanisms as they vary from species to species, from high dose to low dose, and from one route of exposure to another drives the choice of the most appropriate extrapolation approach. Thus, in the new guidelines, the dose–response extrapolation procedure follows conclusions about mode of action in the hazard assessment. The term *mode of action* is deliberately chosen in these new guidelines in lieu of *mechanism* to indicate using knowledge that is sufficient to draw a reasonable working conclusion without having to know the processes in detail, as the term *mechanism* might imply. Although an induced adverse effect may result from a complex and diverse process, a risk assessment must operationally dissect the presumed

critical events, at least those that can be measured experimentally, to derive a reasonable approximation of human risk.

1. Default Extrapolation Approaches

The LMS procedure of the 1986 guidelines (1) for extrapolating risk from upper-bound confidence intervals is no longer recommended as the linear default in the 1996 proposed guidelines (2). The linear default in the new guidelines is a straight-line extrapolation to the origin (i.e., zero dose, zero extra risk) from the point of departure (i.e., the LED_{10}) identified in the range of observed data (Figure 3). The new linear default approach does not imply unfounded sophistication as extrapolation with the LMS procedure does. The linear default approach would be considered for agents that directly affect growth control at the DNA level (e.g., carcinogens that directly interact with DNA and produce mutations). There might be modes of action other than DNA reactivity that are better supported by the assumption of linearity. When inadequate or no information exists to explain the carcinogenic mode of action of an agent, the linear default approach would be used as a science policy choice in the interest of public health. Likewise, a linear default would be used if evidence demonstrates the lack of support for linearity (e.g., lack of direct DNA reactivity and mutagenicity) and there is also an absence of sufficient information on another mode of action to explain the induced tumor response. The latter is also a public health protective policy choice.

Although the understanding of the mechanisms of induced carcinogenesis likely will never be complete for most agents, there are situations for which evidence is sufficient to support an assumption of nonlinearity. Because it is experimentally difficult to distinguish modes of actions with true "thresholds" from others with a nonlinear dose-response relationship, the proposed nonlinear default procedure is considered a practical approach to use without the necessity of distinguishing sources of nonlinearity. In the 1996 proposed cancer guidelines (2), the nonlinear default approach begins at the identified point of departure and provides a margin-of-exposure (MoE) analysis rather than estimating the probability of effects at low doses (Figure 3). The MoE analysis is used to compare the point of departure with the human exposure levels of interest. The MoE is the point of departure divided by the environmental exposure of interest. The key objective of the MoE analysis is to describe for the risk manager how rapidly responses may decline with dose. A shallow slope suggests less reduction than a steep one. The steepness of the slope of the dose-response curve is also an important consideration in noncancer risk assessments applying the BMD approach. Information on factors such as the nature of response being used for point of departure (i.e., tumor data or a more sensitive precursor response) and biopersistence of the agent are important to consider in the MoE analysis. As a default assumption for two of these points, a numerical factor of no less than 10 each may be used to account for human variability and for interspecific differences in sensitivity when humans may be more sensitive than animals. When human

are found to be less sensitive than animals, a default factor of no smaller than 0.1 may be used to account for this.

A nonlinear default position must be consistent with the understanding of the agent's mode of action in causing tumors. For example, a nonlinear default approach would be taken for an agent's causing tumors as a secondary consequence of organ toxicity or induced physiological disturbances (e.g., antithyroid agents that perturb pituitary-thyroid homeostasis, as discussed earlier). Because there must be a sufficient understanding of the agent's mode of action to take the nonlinear default position, it is anticipated that the modeling of precursor responses to tumor development will play an important role in providing support for nonlinearity, or modeling may actually be used instead of tumor data for determining the point of departure for the MoE analysis (see Section III.C).

There may be situations for which it is appropriate to consider both linear and nonlinear default procedures. For example, an agent may produce tumors at multiple sites by different mechanisms. In another case, for example, when it is apparent that an agent is both DNA reactive and highly active as a promoter at higher doses, both linear and nonlinear default procedures may be used to distinguish between the events operative at different portions of the dose-response curve and to consider the contribution of both phenomena. For example, formaldehyde, which was discussed earlier, is DNA reactive at low doses and active as a promoter at higher doses (i.e., concentrations of formaldehyde that cause cytotoxicity and increased cell proliferation are also carcinogenic in the nose).

There may be situations for which there is insufficient data to provide high confidence in a conclusion about any single mode of action of a given agent and for which different mechanisms may be operating at the different sites of tumor induction. Although the available data generally supports nonlinearity, a linear mechanism (e.g., a mutagenic metabolite for one of the tumor sites) cannot be entirely dismissed. Both defaults are conducted and a discussion of the degree of confidence in each is provided to the risk manager. The linear default may be viewed as conservative (i.e., likely to overestimate the risk at low exposures), and it might be more appropriate for screening analyses. The nonlinear default may be viewed as more representative of the risk given the growth-promoting potential and toxicity of the given agent.

C. Modeling of Precursor Response Data

The proposed EPA cancer guidelines (2) call for modeling of not only tumor data in the observable range but other responses thought to be important precursor events in the carcinogenic process (e.g., DNA adducts, gene or chromosomal mutation, cellular proliferation, hyperplasia, hormonal or physiological disturbances, receptor binding). The modeling of important precursor response data makes extrapolation based on default procedures, discussed earlier, more meaningful by providing insights into the relationships of exposure and tumor response below the observable range. In addition, modeling of nontumor data may provide support for selecting a certain extrapolation procedure (linear vs. nonlinear). If the nontumor endpoint is believed to be part of a continuum that leads to

tumors, such data could then be used to extend the dose–response curve below the observed tumor response to provide insight into the low–dose response range. For example, studies using DNA adducts can be conducted with doses overlapping with the observed tumors down to environmental exposure levels. Several studies have demonstrated the merit of examining the relationship between DNA adduct concentration and tumor incidence for more accurate low-dose extrapolations (reviewed in Ref. (75)). However, when using DNA adducts (as a dosimeter) to extend the observable range, it is important to have a reasonable understanding of the target cell and the adduct involved in the carcinogenic process. In addition, changes in cell proliferation rates can cause a steep upward curvature of the dose–response curve, and thus need to be factored into the evaluation of risk. The role of cell proliferation in changing the cancer dose–response curve has been shown for 2-acetylaminofluorene for bladder tumors (76) and for formaldehyde for nasal tumors (28).

Precursor response data may be modeled and used for extrapolation instead of the available tumor data. Currently, it is not anticipated that precursor response data will be used in lieu of tumor data for many compounds because of the more stringent conditions that must be demonstrated. To be acceptable for extrapolation, the mode of action and the role the precursor event plays in the carcinogenic process must be understood. Furthermore, the precursor response should be considered to be more informative of the agent's carcinogenic risk. Precursor data should be from in vivo experiments and from repeat dosing experiments over an extended period of time; precursor data are most

valuable if they are built into the design of the cancer bioassay. It is anticipated that the modeling of precursor response data will come into play predominantly for the nonlinear default approach, which must be based on a reasonable understanding of the agent's mode of action in causing tumors. The most likely situations for which precursor response data are used to estimate risk involve those mechanisms for which tumor development is secondary to toxicity or disruption of a physiological process. For example, hyperplasia might be used in lieu of tumor data to extrapolate risk for a bladder carcinogen that causes calculi to form in the urine, or TSH levels might be used for a thyroid carcinogen that perturbs hypothalamus-pituitary-thyroid homeostasis. Alterations in TSH or thyroid hormone levels may result in other disease consequences. Early responses in the continuum of events that lead to organ pathology or resultant diseases, such as liver enzyme changes and liver histopathology, respiratory irritation, and respiratory tract damage, have been a consideration in noncancer risk assessment (66). Thus, the consideration of precursor response data in health risk assessment is not a new concept.

IV. Emerging Directions in Exposure Assessment

Exposure is defined as the contact of a chemical, physical, or biological agent with the outer boundary of an organism (7). Application of exposure data to the field of risk assessment has grown in importance since the early 1970s because of greater public, academic, industrial, and government awareness of chemical pollution problems in the environment. In environmental health assessment one attempts to address the question of

how many people are exposed to a pollutant and to how much. Information about the distribution of exposure to determine the causes of exposures for high risk groups is a key element in the development of cost-effective mitigation strategies. In addition, information is needed on body burden and related factors in the general population to provide a baseline for interpreting the public health significance of measured exposures from site- or source-specific investigations. For example, body burden levels of environmental pollutants can put people near the linear part of the dose-response curve, even for a dose-response curve that is nonlinear.

A current trend in health risk assessment is to assess cumulative total exposures and risks to multiple environmental agents, through multiple pathways and routes. People are exposed to many chemicals via different pathways during their lives. Multichemical exposures are ubiquitous (e.g., air and soil pollution from municipal incinerators, leakage from hazardous waste facilities and uncontrolled waste sites, drinking water containing chemical substances formed during disinfections). Because of the difficulties in assessing multiple exposures, assessments have tended to focus on a single chemical and often on a single pathway of exposure. Little is known about whether exposure to one chemical or class of chemicals is correlated with exposure to other chemicals; and even less is known about the combined risks associated with multiple exposures. Thus, risk assessments of mixtures usually involve substantial uncertainties. A common risk assessment practice is to evaluate toxicological properties of the components of mixture and assume that similar effects are additive. However, some research indicates that toxicological interactions

among chemicals can be antagonistic or synergistic. Pharmacokinetic studies or newer technologies using transgenic animals (fish or rodents) may make studies of mixtures (e.g., binary, tertiary, or quantinary combinations of chemicals) more practical than traditional toxicology animal bioassays. Moreover, research using in vitro or in vivo eukaryotic models of the combined effects of mixtures of environmental contaminants on elements of cell cycle control—including growth, death, and differentiation—may provide insight into combined risk of chemicals representative of mixtures that are found in environmental media.

V. Emphasis on Risk Characterization

Risk assessment is an integrative process that culminates ultimately into a risk characterization summary. Risk characterization is the final step of the risk assessment process in which all preceding analyses (from hazard assessments to dose–response assessments to exposure assessments) are tied together to convey the overall conclusions about potential human risk). This component of the risk assessment process characterizes the data in nontechnical terms, explaining the key issues and conclusions of each component of the risk assessment and the strengths and weaknesses of the data. Risk characterization is the product of risk assessment that is used in risk management decisions. The current emphasis on risk characterization is illustrated by recent publications by the EPA and the National Academy of Science/National Research Council (77)(78).

VI. Summary

Compared with traditional approaches to health risk assessment, ongoing activities to assess the risk of environmental agents are including a more complete discussion of the issues and an evaluation of all relevant information, promoting the use of mode-of-action information to reduce the uncertainties associated with using experimental data to characterize and project how human beings will respond to certain exposure conditions. This emphasis on mechanisms is to promote research and testing to improve the scientific basis of health risk assessment and stimulate thinking on how such information can be applied. As the science continues to evolve the practice and policies of risk assessment will reflect these advances.

Figure Captions

Figure 1. The elements of the risk paradigm: health risk assessment is organized by the paradigm put forward by the National Academy of Sciences (79)(10), which defines four types of analysis: hazard assessment, dose-response assessment, exposure, and risk characterization.

Figure 2. The risk characterization process: the framework of the EPA 1996 *Proposed Guidelines for Carcinogen Risk Assessment* (2) is based on the paradigm put forth by the National Academy of Sciences (10). This framework puts an emphasis on characterizations of hazard, dose-response, and exposure assessments. These technical characterizations integrate the analyses of hazard, dose-response and exposure, explain the weight of evidence and strengths and weaknesses of the data, as well as discusses the issues and uncertainties surrounding the conclusions. The technical characterizations themselves are integrated into the overall conclusions of risk which are presented in a risk characterization summary (from (2)(11)).

Figure 3. Dose-Response Assessment: the current trend for dose-response (DR) assessment of cancer and noncancer endpoints is to begin with modeling response data in the observable range (2)(70). In the of the EPA 1996 *Proposed Guidelines for Carcinogen Risk Assessment* (2) DR is proposed as a two-step process; in the first step, response data are modeled in the range of observation, and in the second step, the point of

departure below the range of observation is determined. The LED_{10} (effective dose corresponding to the lower 95% limit on a dose associated with 10%increase in response) is proposed as a point of departure for extrapolation to the origin as the linear default or for a margin of exposure analysis as the nonlinear default (from (2)(11)).

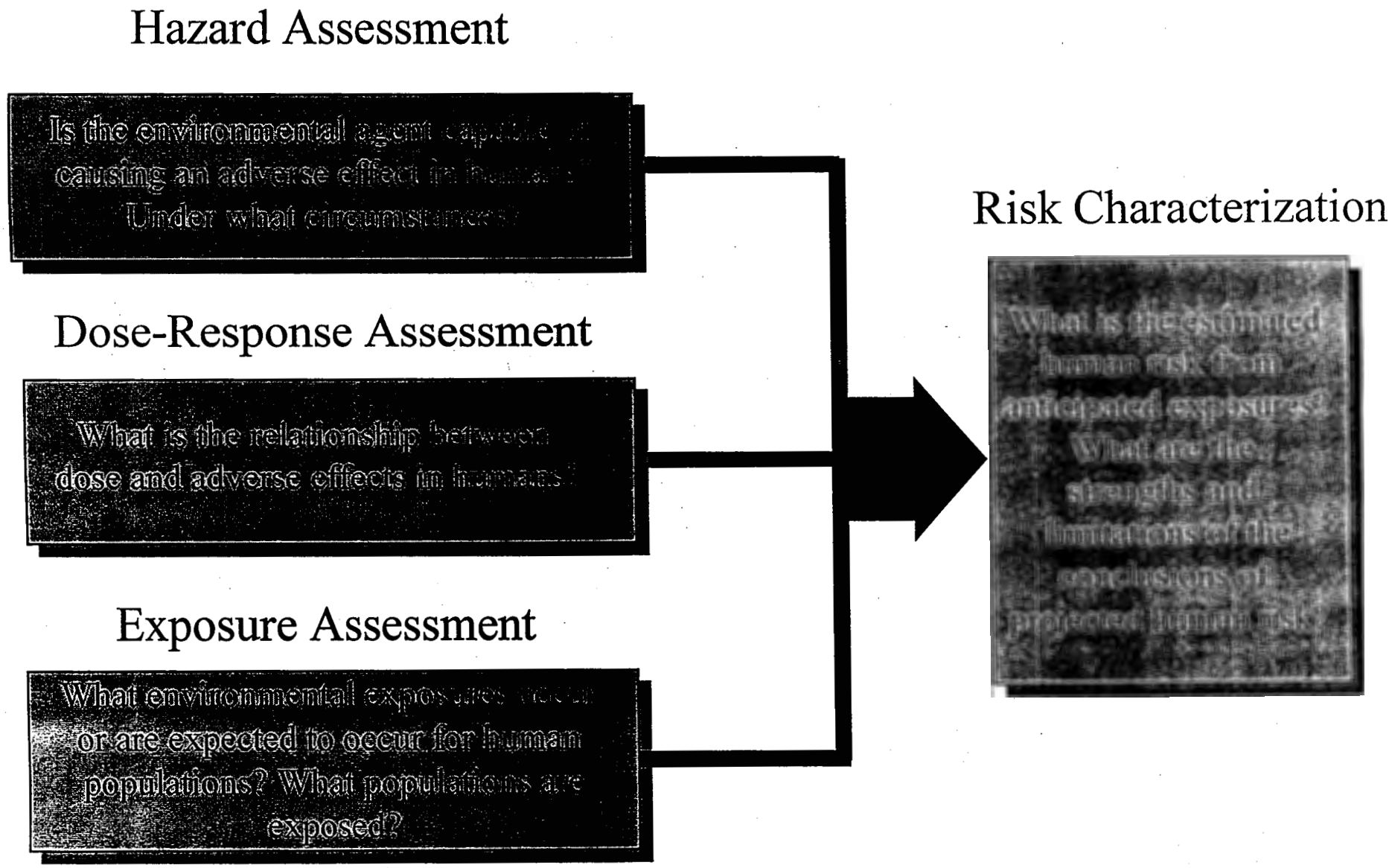
Hazard Assessment
Is the environmental agent capable of causing an adverse effect in humans? Under what circumstances?
Dose-Response Assessment
What is the relationship between dose and adverse effects in humans?
Exposure Assessment
What environmental exposures occur or are expected to occur for human populations? What populations are exposed?
Risk Characterization
What is the estimated human risk from anticipated exposures? What are the strengths and limitations of the conclusions of projected human risk?

Figure 1.

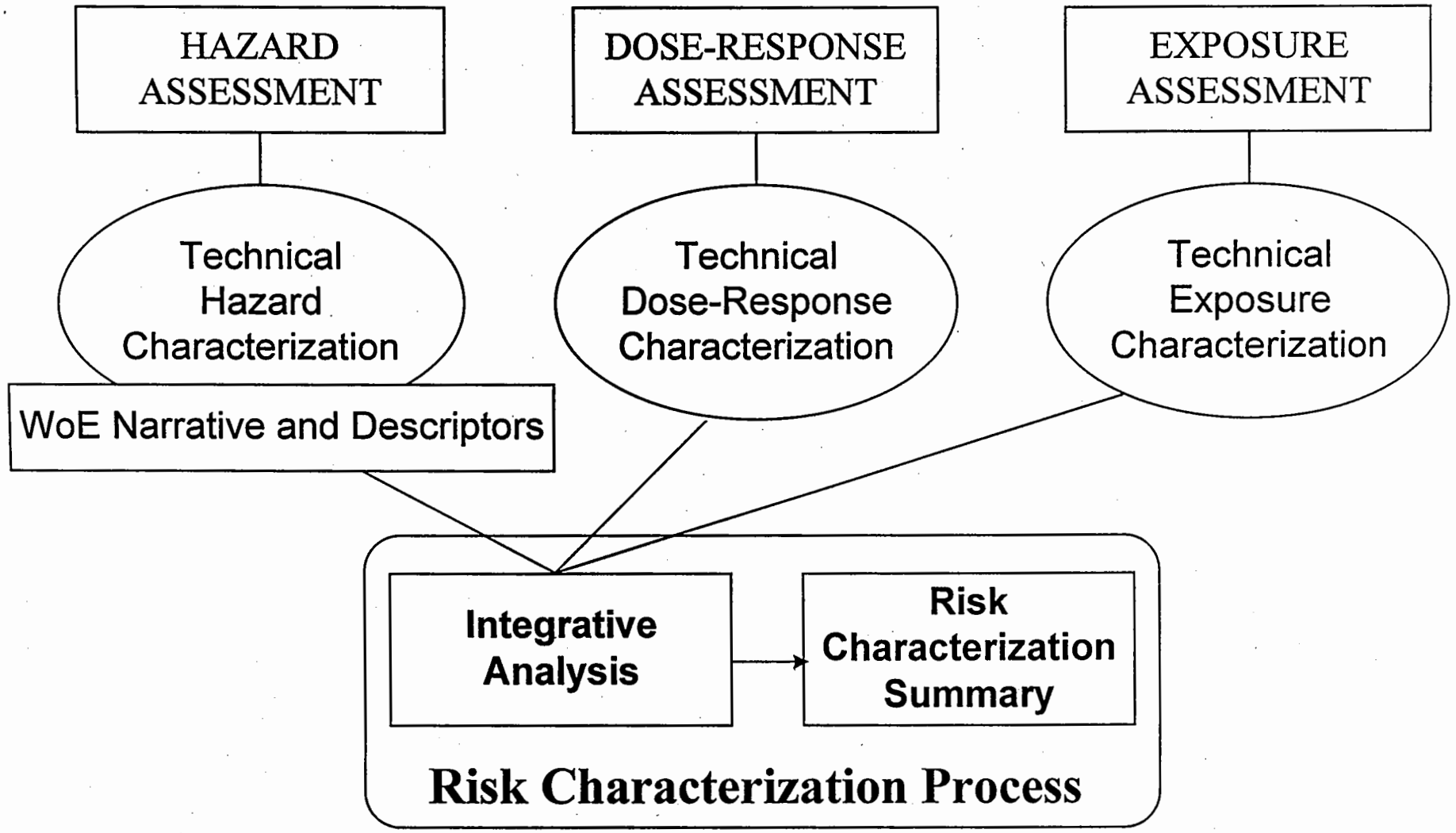
HAZARD ASSESSMENT
DOSE-RESPONSE ASSESSMENT
EXPOSURE ASSESSMENT
Technical Hazard Characterization
Technical Dose-Response Characterization
Technical Exposure Characterization
WoE Narrative and Descriptors
Integrative Analysis
Risk Characterization Summary
Risk Characterization Process

Figure 2.

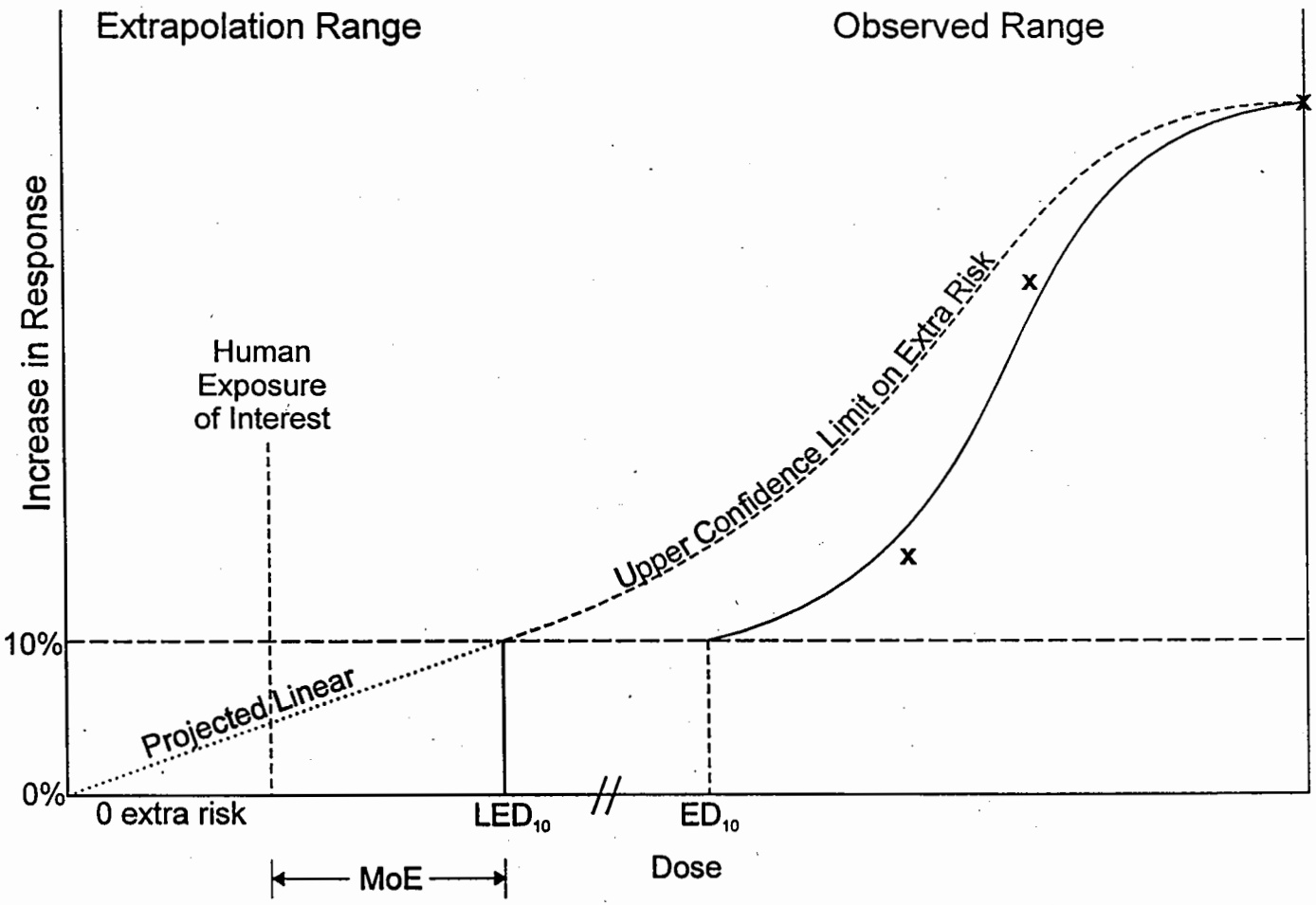
Extrapolation Range
Observed Range
Increase in Response
Human
Exposure
of Interest
Upper Confidence Limit on Extra Risk
10%
Projected Linear
0%
0 extra risk
LED10
ED10
MoE
Dose

Figure 3.

Table 1. Current Trends in Health Risk Assessment

Historical Approach	→	Emerging Emphasis
Phenomenological studies		Mechanism studies
Separate assessments and approaches for cancer and noncancer risks		Integrative health assessments and harmonization of approaches for cancer and noncancer risks
Risk to general population		Risk to sensitive subpopulations
Single chemical exposure and single pathway		Multiple chemical exposure via multiple pathways
Risk characterization		More expanded characterizations of human risk

References

1. U.S. Environmental Protection Agency, Guidelines for carcinogen risk assessment, Fed. Reg. 51(185):33992-34003 (1986).

2. U.S. Environmental Protection Agency, Proposed guidelines for carcinogen risk assessment, Fed. Reg. 61(79):17960-18011 (1996).

3. U.S. Environmental Protection Agency, Guidelines for mutagenicity risk assessment, Fed. Reg. 51(185):34006-340012 (1986).

4. U.S. Environmental Protection Agency, Guidelines for developmental toxicity risk assessment (notice), Fed. Reg. 56(234):63798-63826 (1992).

5. U.S. Environmental Protection Agency, Reproductive toxicity risk assessment guidelines, Fed. Reg. 61(212):56274-56322 (1996).

6. U.S. Environmental Protection Agency, Proposed guidelines for neurotoxicity risk assessment, Fed. Reg. 60(192):52032-52056 (1995).

7. U.S. Environmental Protection Agency, Guidelines for exposure assessment (notice), Fed. Reg. 57(104):22888-22896 (1991).

8. U.S. Environmental Protection Agency, Guidelines for the health risk assessment of chemical mixtures, Fed. Reg. 51(185):34014-34025 (1986).

9. U.S. Environmental Protection Agency, Environmental health threats to children, EPA175F-96-001, Office of the Administrator, U.S. Environmental Protection Agency, Washington, DC, Sep. 1996.

10. National Research Council, Science and judgment in risk assessment, committee on risk assessment of hazardous air pollutants, Commission on Life Sciences, National Research Council, National Academy Press, Washington, DC, 1994).

11. J. Wiltse and V.L. Dellarco, The U.S. Environmental Protection Agency guidelines for carcinogen risk assessment: past and future, Mutat. Res. 365:3-16 (1996).

12. J.A. Swenberg, B. Short, S. Borghoff, J. Strasser, and M. Charbonneau,The comparative pathobiology of $\alpha_2\mu$-globulin nephropathy. Toxicol. Appl.Pharmacol. 97:35-46 (1989).

13. L.D. Lehman-McKeeman, M.I. Rivera-Torres, and D. Caudill, Lysosomal degradation of $\alpha 2\mu$-globulin and $\alpha 2u$-globulin-xenobiotic conjugates, Toxicol. Appl. Pharmacol. 103:539-548 (1990).

14. D.R. Dietrich, and J.A. Swenberg, The presence of $\alpha 2\mu$-globulin is necessary for *d*-limonene promotion of male rat kidney tumors. Cancer Res. 51:3512-3521 (1991).

15. U.S. Environmental Protection Agency, Alpha 2u-globulin: association with chemically induced renal toxicity and neoplasia in the male rat, Risk Assessment Forum, Washington DC, EPA/625/3-91/019f, Sep. 1991, 118 pp.

16. R.L. Melnick, M.C. Kohn, and C.J. Portier, Implications for risk assessment of suggested nongenotoxic mechanisms of chemical carcinogenesis, Environ. Health Perspect. 104:123-134 (1996).

17. R.N. Hill, L.S. Erdreich, O.E. Paynter, et al., Review: thyroid follicular cell carcinogenesis, Fund. Appl. Toxicol. 12:629-697 (1989).

18. R.M. McClain, The significance of hepatic microsomal enzyme induction and altered thyroid function in rats: Implications for thyroid gland neoplasia. Toxicol. Pathol. 17:294--306 (1989).

19. R.M. McClain, Thyroid gland neoplasia: non-genotoxic mechanisms, Toxicol. Lett. 64/65:397-408 (1992).

20. U.S. Environmental Protection Agency, Draft risk assessment forum thyroid cancer policy report, March 4, 1996.

21. R.M. McClain, The use of mechanistic data in cancer risk assessment: Case example-sulfonamides, in Low-Dose Extrapolation of Cancer Risks: Issues and Perspectives, S. Olin, W. Farland, C. Park, L. Rhomberg, R. Scheuplein, T. Starr and J. Wilson (eds.), ILSI Press, Washington, DC, pp.163-173.

22. S.M. Cohen and L.B. Ellwein, Genetic errors, cell proliferation and carcinogenesis, Cancer Res. 51:6493-6505 (1991).

23. U.S. Environmental Protection Agency, Melamine: toxic chemical release reporting, Fed. Reg. 53:23128-23132 (1988).

24. W.D. Kerns, K.L. Pavkov, D.J. Donofrio, E.J. Gralla, and J.A. Swenberg, Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure, Cancer Res., 43:4382-4392 (1983).

25. O. Hernandez, L. Rhomberg, K. Hogan, C. Siegel-Scott, D. Lai, G. Grindstaff, M. Henry, and J.A. Cotruvo, Risk assessment of formaldehyde, J. Hazard. Mat. 39:161-172 (1994).

26. M. Casanova, K.T. Morgan, W.H. Steinhagen, J.I. Everitt, J.A. Popp, and H.d'A. Heck, Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of rhesus monkeys: pharmacokinetics, rat-to-monkey interspecies scaling, and extrapolation to man, Fund. Appl. Toxicol. 17:409-428 (1991).

27. M. Casanova, K.T. Morgan, E.A. Gross, O.R. Moss, and H.d'A. Heck, DNA-protein cross-links and cell replication at specific sites in the nose of F344 rats exposed subchronically to formaldehyde, Fund. Appl. Toxicol. 23:525-536 (1994).

28. H.d'A. Heck, M. Casanova, and T.B. Starr, Formaldehyde toxicity-new understanding. Crit. Rev. Toxicol. 20:397-426 (1990).

29. T.M. Monticello, J.A. Swenberg, E.A. Gross, J.R. Leininger, J.S. Kimbell, S. Seilkop, T.B. Starr, J.E. Gibson, and K. T. Morgan, Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells, Cancer Res. 56:1012-1022 (1996).

30. M.S. Bogdanffy, H.C. Dreef-van der Meulen, R.B. Beems, V.J. Feron, R.W. Rickard, T.R. Tyler, and T.C. Cascieri, Chronic toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse, Fund. Appl. Toxicol. 23:215-229 (1994).

31. M.S. Bogdanffy, T.R. Tyler, M.B. Vinegar, R.W. Capanini, and T.C. Cascieri, Chronic toxicity and oncogenicity study with vinyl acetate in the rat: in utero exposure in drinking water, Fund. Appl. Toxicol. 23:206-214 (1994).

32. B.R. Blakley, Enhancement of urethane-induced adenoma formation in Swiss mice exposed to methyl mercury, Can. J. Comp. Med. 48:299-302 (1984).

33. International Agency for Research on Cancer, Occupational exposure to mists and vapors from strong inorganic acids and other industrial chemicals, Lyon, France, vol. 54:237287 (1992).

34. National Toxicology Program. 1991. Toxicology and carcinogenesis studies of 1,3-butadiene in B6C3F1 mice (inhalation). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NTP TR434. NIH publication number 92-3165.

35. A.R. Dahl, W.E. Bechtold, and J.A. Bond, Species difference in the metabolism and disposition of inhaled 1,3-butadiene and isoprene, Environ. Health Perspect. 86:65-69 (1990).

36. A.R. Dahl, D.J. Sun, L.S. Birnbaum, et al., Toxicokinetics of inhaled 1,3-butadiene in monkeys: comparison to toxicokinetics in rats and mice, Toxicol. Appl. Pharmacol. 110:9-19 (1991).

37. G.A. Csanady, F.P. Guengerich, and J.A. Bond, Comparison of the biotransformation of 1,3-butadiene and its metabolite, butadiene monoepoxide, by hepatic and pulmonary tissue from humans, rats, and mice, Carcinogenesis 13:1143-1153 (1992).

38. E. Delzell, N. Sathiakumar, A. Macaluso, et al., A follow up study of synthetic rubber workers. Submitted to the International Institute of Synthetic Rubber Producers, Department of Epidemiology, University of Alabama at Birmingham, Oct. 2, 1995.

39. F.J. Gonzalez, The role of carcinogen-metabolizing enzymes polymorphisms in cancer susceptibility, Reprod. Toxicol. (in press).

40. M. Kihara and K. Noda, Risk of smoking for squamous and small cell carcinomas of the lung modulated by combinations of CYP1A1 and GSTM1 gene polymorphisms in a Japanese populations, Carcinogenesis 16:2331-2336 (1995).

41. K. Nakachi, K. Imai, S. Hayashi, and K. Kawajiri, Polymorphisms of the CYP1A1 and glutathione S-transferase genes associated with susceptibility to lung cancer in relations to cigarette dose in a Japanese population, Cancer Res. 53:2994-2999 (1993).

42. M.J. Khoury, M. Gomez-Farias, and J. Mulinare, Does maternal cigarette smoking during pregnancy cause cleft lip and palate in offspring? Am. J. Dis. Child. 143:333-337 (1989).

43. H.H. Ardinger, K.H. Buetow, and G.I. Bell, Association of genetic variation of the transforming growth factor-alpha gene with cleft lip and palate, Am. J. Hum. Genet. 45:348-53 (1989).

44. World Health Organization, Environmental health criteria 101: Methylmercury, Geneva, Switzerland, 1990.

45. U.S. Environmental Protection Agency, Integrated risk information system (IRIS): online, rfd/rfc document for methylmercury, National Center for Environmental Assessment, Washington DC, 1995.

46. R.A. Goyer, Results of lead research: prenatal exposure and neurological consequences, Environ. Health Perspect. 104:1050-1054 (1996).

47. U.S. Environmental Protection Agency, Proposed regulation, Fed. Reg. 59(170):45871 (1994).

48. U.S. Department of Housing and Urban Development, Guidelines for the evaluation and control of lead-based paint hazards in housing, HUD-1539-LBP, U.S. Department of Housing and Urban Development, Washington, DC, 1995.

49. Center for Disease Control, Strategic plan for the elimination of childhood lead poisoning, U.S. Department of Health and Human Services, Washington, DC, 1991.

50. J. Schwartz, D. Slater, T.V. Larson, W.E. Pierson, and J.Q. Koenig, Particulate air pollution and hospital emergency room visits for asthma in Seattle, Am. Rev. Respir. Dis. 147:826-831 (1993).

51. P.H.N. Saldiva, C.A. Pope III, J. Schwartz J, et. al., Air pollution and mortality in elderly people: a time-series study in Sao Paulo, Brazil, Arch. Environ. Health 50:159-163 (1995).

52. B. Ostro, J.M. Sanchez, C. Aranda, and G.S. Eskeland, Air pollution and mortality: results from a study of Santiago, Chile (papers from the ISEA-ISEE annual meeting, September 1994, Research Triangle Park, NC, M. Lippman, ed.), J. Exposure Anal. Environ. Epidemiol. (in press).

53. U.S. Environmental Protection Agency, Air Quality Criteria for Particulate Matter, EPA/600/P-95/001bF, Vol. 2, Office of Research and Development, Washington, DC, 1996.

54. U.S. Environmental Protection Agency, Air Quality Criteria for Ozone and Related Photochemical Oxidants, EPA/600/P-93/004aF, Vol. 3, Office of Research and Development, Washington, DC, 1996.

55. N.I. Kerkvliet, Immunotoxicology of dioxin and related chemicals, Dioxins and Health (A. Schecter, ed.), Plenum Press, New York, 1994, pp. 199-218.

56. H.M. Theobald and R.E. Person, Developmental and reproductive toxicity of dioxin and other A*h* receptor agonists, Dioxin and Health (A. Schecter, ed.), Plenum Press, New York, pp. 309-335, 1994.

57. U.S. Environmental Protection Agency, Health assessment document for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds: external review draft, EPA/600/BP-92/001c, Vol. 3, Office of Research and Development, Washington, DC, 1994.

58. A.M. Scheuhammer, Effects of acidification on the availability of toxic metals and calcium to wild birds and mammals, Environ. Pollut. 71:329-375 (1991).

59. A.M. Scheuhammer and P.J. Blancher, Potential risk to common loons (*Gravia immer*) from methylmercury exposure in acidified lakes, Hydrobiologia 279-289:445-455 (1994).

60. E. Carlsen, A. Giwercman, N. Keiding, and N.E. Skakkebaek, Evidence for decreasing quality of semen during past 50 years, Br. Med. J. 305:609-613 (1992).

61. W.R. Kelce, C.R. Stone, S.C. Laws, L.E. Gray, et. al., Persistent DDT metabolite p,p-DDE is a potent androgen receptor antagonist, Nature 375:581-585 (1995).

62. National Research Council, Animals as sentinels of environmental health hazards, Committee on Animals as Monitors of Environmental Hazards, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, National Academy Press, Washington, DC, 1991.

63. K.S. Crump, An improved procedure for low-dose carcinogenic risk assessment from animal data. J. Environ. Pathol. Toxicol. 5:675 (1981).

64. D. Krewski, D.W. Gaylor, and W.K. Lutz, Additivity to background and linear extrapolation, in: Low-Dose Extrapolation of Cancer Risks: Issues and Perspectives, S. Olin, W. Farland, C. Park, L. Rhomberg, R. Scheuplein, T. Starr and J. Wilson (Eds.), ILSI Press, Washington, DC, pp. 105-121(1995).

65. A.M. Jarabek, Interspecies extrapolation based on mechanistic determinants of chemical disposition, J. Hum. Ecol. Risk Assess. 1(5):641-662 (1995).

66. U.S. Environmental Protection Agency, Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry, EPA/600/8-90/066F, Office of Research and Development, Washington, DC, 1994.

67. D.G. Barnes and M.L. Dourson, Reference dose (RfD): description and use in health risk assessments, Reg. Toxicol. Pharmacol. 8:471-488 (1988).

68. A.M. Jarabek, M.G. Menache, J.H. Overton, M.L. Dourson, and F.J. Miller F.J., The U.S. Environmental Protection Agency's inhalation RfD methodology: risk assessment for air toxics, Toxicol. Ind. Health 6:279-301 (1990).

69. A.M. Jarabek, The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches, Toxicol. Lett. 79:171-184 (1995).

70. U.S. Environmental Protection Agency, The use of the benchmark dose approach in health risk assessment, EPA/630/R-94/007, Office of Research and Development, Washington, DC, 1995.

71. B.C. Allen, P.L. Strong, C.J. Price, S.A. Hubbard, and G.P. Daston, Benchmark dose analysis of developmental toxicity in rats exposed to boric acid, Fund. Appl. Toxicol. (in press).

72. D.G. Barnes, G.P. Daston, J.S. Evans, A.M. Jarabek, R.J. Kavlock, C.A. Kimmel, C. Park, and H.L. Spitzer, Benchmark dose workshop: criteria for use of a benchmark dose to estimate a reference dose, Reg. Toxicol. Pharmacol. 21:296-306 (1995).

73. R.J. Kavlock, J.E. Schmid, R.W. Setzer Jr, A simulation study of the influences of study design on the estimation of benchmark doses for developmental toxicity, Risk Anal. 16:391-403 (1996).

74. C. Chen and W. Farland, Incorporating cell proliferation in quantitative cancer risk assessment: approaches, issues, and uncertainties, in: B. Butterworth, T. Slaga, W. Farland and M. McClain (Eds.), Chemical Induced Cell Proliferation: Implications for Risk Assessment, Wiley-Liss, New York, pp. 481-499 (1991).

75. D.K. La, and J.A. Swenberg, DNA adducts: biological markers of exposure and potential applications to risk assessment, Mutat. Res. 365:129-146 (1996).

76. S.M. Cohen and L.B. Ellwein, Proliferative and genotoxic cellular effects in 2-acetylaminofluorene bladder and liver carcinogenesis: biological modeling of the ED01 study, Toxicol. Appl. Pharmacol. 104:79-93 (1990).

77. U.S. Environmental Protection Agency, Policy for risk characterization, memorandum of Carol M. Browner, Administrator, March 21, 1995, Washington, DC, 1995.

78. National Research Council,. Understanding Risk: Informing decisions in a democratic Society. Committee of Risk Characterization, Commission on behavioral and Social Sciences and Education, National Academy Press, Washington DC, 249 pages (1996).

79. National Research Council, Risk Assessment in the Federal Government: Managing the Process, Committee on the Institutional Means for Assessment of Risks to Public Health, Commission on Life Sciences, NRC, National Academy Press, Washington, DC. (1983).

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15. SUPPLEMENTARY NOTES

16. ABSTRACT

Health risk assessment practices are evolving on a number of fronts. Risk analyses have historically relied to a large degree on observations of frank toxic effects. Risk assessments are moving from this phenomenologic approach by identifying the ways environmental agents are changed through metabolic processes, the dose at the affected organ system, and how an agent produces its toxic effect is beginning to break down the dichotomy that existed between assessments of cancer and noncancer risks. Of equal importance, the "one-size-fits-all" approach is being replaced by emphasizing the ascertainment of risk to susceptible subpopulations. EPA recently put forth a new national agenda to protect children from toxic agents in the environment (1). In addition, to make risk assessments more understandable and useful, there is an increased emphasis on risk characterization. Risk characterization is the final output of the risk assessment process from which all preceding analyses (i.e., from the hazard, dose-response, and exposure assessments) are tied together to convey in nontechnical terms the overall conclusions about potential human risk, as well as the rationale, strengths, and limitations of the conclusions. This article discusses several trends occurring in risk assessment in the context of the risk paradigm-hazard, dose-response, and exposure assessments and subsequent risk characterization. Chemical examples are provided to illustrate these emerging directions in health risk assessment.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

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