United States
Environmental Protection
Agency

Office of Research and
Development
Washington DC 20460

EPA/630/R-94/005a
November 1994

EPA

Report on the Workshop on Cancer Risk Assessment Guidelines Issues

RISK ASSESSMENT FORUM

EPA/630/R-94/005a
November 1994

REPORT ON THE WORKSHOP ON

CANCER RISK ASSESSMENT GUIDELINES ISSUES

Prepared by:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02173
EPA Contract No. 68-D9-0133

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC

NOTICE

Mention of trade names or commercial products does not constitute endorsement or recommendation for use. Statements are the individual views of each workshop participant; none of the statements in this report represent analyses or positions of the Risk Assessment Forum or the U.S. Environmental Protection Agency (EPA).

This report was prepared by Eastern Research Group, Inc. (ERG), an EPA contractor, as a general record of discussions during the Workshop on Cancer Risk Assessment Guidelines Issues. As requested by EPA, this report captures the main points and highlights of discussions held during plenary sessions and includes brief summaries of the breakout group sessions. The report is not a complete record of all details discussed, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. In particular, each of the four breakout group summaries was prepared at the workshop by individual breakout group chairs based on their groups' discussions during the workshop. Thus, there may be slight differences between the four groups' recommendations.

CONTENTS

CONTENTS (cont.)

FOREWORD

This report includes information and materials from a technical review workshop organized by the U.S. Environmental Protection Agency's (EPA's) Risk Assessment Forum (RAF) and Office of Health and Environmental Assessment (OHEA). The meeting was held in Reston, Virginia, at the Hyatt Regency on September 12-14, 1994. The subject of the technical review was the document entitled *Revisions to the Guidelines for Carcinogen Risk Assessment* (External Review Draft, EPA/600/BP-92/003). A copy of this report can be obtained through EPA's Office of Research and Development publications office, CERI, U.S. EPA, 26 West Martin Luther King Drive, Cincinnati, Ohio 45268 (513-569-7562). The expert technical reviewers were convened to independently comment on the draft guidelines and make recommendations intended to enhance the guidelines development process as well as the ultimate product.

Notice of the workshop was published in the *Federal Register* on August 22, 1994 (59 FR 43125). The notice invited members of the public to attend the workshop as observers and provided logistical information to enable observers to preregister. Over 100 observers attended the workshop, including representatives from federal government, industry, environmental and health organizations, the press, trade organizations, consulting firms, law firms, and public interest groups, as well as interested citizens.

In outlining the scope of the technical review, EPA emphasized that the draft guidelines revisions are in a preliminary stage of development and should not be construed as a policy statement. EPA explained that the proposed revisions would lead to some changes in current Agency cancer risk assessment practices. EPA explained further that because the draft guidelines have received only limited review within the Agency, they could benefit greatly from the comments and recommendations of outside experts. EPA asked the expert reviewers to concentrate their review on technical issues concerning mode of action, hazard identification, dose response, and default assumptions.

A balanced group of expert technical reviewers were selected from academia, industry, and government. Selected reviewers provided scientific expertise in the following disciplines: toxicology, epidemiology, public health, biostatistics, risk assessment/risk management policy, cancer biology, and mechanisms of carcinogenesis.

In workshop discussions, EPA sought comments from these scientific experts on the draft revision of the cancer risk assessment guidelines. The draft guidelines present familiar concepts presented in the 1986 cancer risk assessment guidelines along with innovative approaches for conducting thorough analyses of reliable data on a case-by-case basis, for considering alternative positions, and for developing rationales for major judgments. EPA will use the expert reviewers' comments and recommendations drawn from this technical review workshop in considering revisions to the draft guidelines.

The workshop report is organized as follows. The report opens with a brief introduction concerning the purpose of the workshop and the background of the cancer risk assessment guidelines (section 1). This is followed by a summary of workshop deliberations (section 2). The chairperson's summary is provided next (section 3) and then the four breakout group chairs' summaries (section 4). The last section of the report provides highlights of reviewers' preliminary comments and observers' comments (section 5). Appendices to the workshop report include a list of reviewers, the charge to workshop reviewers, the agenda, reviewer breakout group assignments, and a list of observers.

William Wood, Ph.D.
Executive Director
Risk Assessment Forum

Jeanette Wiltse, Ph.D., J.D.
Deputy Director
Office of Health and Environmental Assessment

SECTION ONE

INTRODUCTION

This report highlights issues and conclusions from a U.S. Environmental Protection Agency (EPA) Risk Assessment Forum and Office of Health and Environmental Assessment (OHEA)-sponsored workshop on reviewing the Agency's *Revisions to the Guidelines for Carcinogen Risk Assessment* (External Review Draft, EPA/600/BP-92/003) published in August 1994. The workshop was convened to gather information from technical expert reviewers that will assist EPA in further developing the draft guidelines.

BACKGROUND

In 1976, EPA published *Interim Procedures and Guidelines for Health Risk Assessments of Suspected Carcinogens* (41 FR 21402). In response to significant advancements in cancer risk assessment approaches and practices as well as the 1983 National Academy of Sciences' (NAS') recommendation that EPA establish guidelines to ensure consistency and technical quality in risk assessments, the Agency convened a task force to further develop the interim guidelines. In September 1986, after several drafts and a peer review by expert scientists, EPA published *Guidelines for Carcinogen Risk Assessment* (51 FR 33992). The stated purpose of the 1986 guidelines was to "guide Agency evaluation of suspect carcinogens in line with the policies and procedures established in the statues administered by EPA." EPA also acknowledged in the guidelines document that future revisions should be undertaken, as appropriate.

Since 1986, our knowledge of carcinogenesis and risk assessment processes have continued to advance, leading EPA to initiate the current revisions to Agency cancer risk assessment practices. A technical panel of EPA's Risk Assessment Forum authored the external review draft guidelines that served as the focus of the September 1994 workshop.

In her introductory remarks at the gathering, Jeanette Wiltse, Ph.D., chair of the Risk Assessment Forum's technical panel, explained the need to revise the 1986 guidelines by highlighting their limitations:

- Hazard identification and the carcinogen classification system do not address:
  - importance of evidence apart from tumor effects
  - route of exposure
  - mode of action
- Dose-response assessment guidance provides only one default mode, which does not recognize the variety of situations encountered and the need to incorporate new information as it becomes available as well as expert judgment.
- Risk characterization is not developed.

Dr. Wiltse also listed the objectives of the guidelines revision effort, which include:

- providing an analytical framework;
- addressing issues to examine and questions to address in the assessment;
- guiding the use of judgment and default assumptions in the assessment; and
- providing flexibility that allows for consideration of scientific advances that cannot yet be described.

The revised guidelines, however, will not be a methods handbook, will not instruct scientists on how to conduct scientific analyses, and will not teach a novice how to conduct a risk assessment. EPA will develop supplementary technical documents as necessary to support issues in the guidelines requiring further explanation.

The major difference in the revised guidelines compared with the 1986 guidelines concerns how evidence is weighed and used in support of decisions. Under the revised guidelines, all empirical evidence will be weighed (i.e., data on animal and/or human tumor effects and other key evidence) and the risk characterization will include a robust qualitative and appropriate quantitative description of the conclusions.

Other differences in the revised risk assessment process will include:

- Hazard characterization:
  - describes the likelihood of hazard to humans and conditions of expression (e.g., route of exposure)
  - uses a hazard narrative instead of, or in addition to, alphanumeric classification
- Dose-response assessment:
  - performed in two steps (i.e., range of observation and range of extrapolation)
  - biologically based model as the first choice for fitting and extrapolation
  - use of both linear and nonlinear defaults

Dr. Wiltse described the workshop as the first step in the process of developing and eventually publishing revised cancer risk assessment guidelines. Following the workshop, the technical panel will revise the draft guidelines. The draft guidelines will then undergo several reviews (i.e., internal EPA review, Risk Assessment Forum review, Science Policy Council review, and other federal reviews) and revision cycles. Then a *Federal Register* proposal and announcement of an EPA Science Advisory Board (SAB) review will be issued. After public and SAB comments are incorporated into the guidelines and the document is given final Agency clearance, the final cancer risk assessment guidelines will be published.

TECHNICAL REVIEW WORKSHOP

To involve outside technical experts in development of the guidelines, EPA's Risk Assessment Forum and OHEA sponsored a three-day workshop, which was held on September 12-14, 1994, at the Hyatt Regency in Reston, Virginia. The meeting gathered 25 experts (see Appendix A for a list of workshop reviewers) with the objectives of identifying and elucidating issues, describing points of view about issues, and highlighting areas for further development by text or illustrative example.

Prior to the workshop, EPA provided each reviewer with a copy of the draft *Revisions to the Guidelines for Carcinogen Risk Assessment* and the 1986 *Guidelines for Carcinogen Risk Assessment.* EPA asked workshop participants to review these materials before the meeting with the following topics in mind:

- mode of carcinogenic action;
- hazard identification;
- low-level dose-response extrapolation;
- observed range dose-response relationships; and
- use of science policy default positions.

See Appendix B for the premeeting charge to workshop reviewers.

Ronald Wyzga, Ph.D., a senior program manager at the Electric Power Research Institute, served as the chairperson of the workshop. In his introductory remarks, Dr. Wyzga reviewed the agenda for the workshop (see Appendix C), providing an explanation of the format for breakout group sessions. Reviewers were divided into four breakout groups according to the following topic areas:

- mode of action;
- default assumptions;
- dose response; and
- hazard identification.

(See Appendix D for reviewer breakout group assignments.) Each breakout group was charged to initially place particular emphasis on their assigned topics; however, the breakout groups were asked to shift their focus on the second day of the workshop to review and report on another breakout group's topic. Dr. Wyzga referred reviewers to the specific questions in the charge (see Appendix C) that particular breakout groups were asked to address in their discussions. To help focus the groups' efforts on addressing each question, Dr. Wyzga reviewed the purpose and goals of the

workshop. He reminded reviewers that the objective was not to reach a consensus on issues, but to identify and elucidate issues relevant to the draft guidelines.

SECTION TWO

SUMMARY OF WORKSHOP DELIBERATIONS

The workshop provided a forum for the expert reviewers to discuss the scientific aspects, thoroughness, and completeness of the draft revisions to the cancer risk assessment guidelines. Workshop participants contributed useful and substantive suggestions and recommendations for improving the draft guidelines. Section 4 of this document provides summaries and recommendations as reported by the chairpersons of the four breakout groups.

All workshop reviewers endorsed the new approach for cancer risk assessment presented in the draft guidelines. The reviewers also supported the emphasis in the draft guidelines on mode of action, thresholds, biologically based models, and biomarkers. Reviewers suggested the following general principles for improving the guidelines:

- Establish a clear process for considering all available scientific information, identifying data gaps, and defining criteria that will govern how assessments will be reevaluated when new scientific information becomes available. Create incentives for generating new information.
- Identify major default assumptions to be used in the absence of data, and develop a rationale for these defaults and a procedure for departing from defaults.
- Expand the discussions on exposure and risk characterization.
- Clarify the role of the guidelines in supporting an iterative process of making decisions based on available data. Explain how various levels of information are required to make different types of regulatory decisions in a tiered risk assessment process.
- Consider a hazard classification scheme incorporating elements proposed by NAS/National Research Council (NRC).

Several expert reviewers expressed the view that the guidelines should explicitly allow for adjustment of the depth of risk assessment and use of default assumptions to accord with the use of the risk assessment. Thus, an early screening assessment for prioritizing would contain more

default assumptions than a more data-rich assessment for a more important decision. In this regard, reviewers also voiced some reservations about the use of multiple plausible default extrapolation procedures for making management decisions. Other reviewers countered that multiple defaults give risk assessors the opportunity to choose between conducting a science-intensive effort or an expedited effort based on the availability of data. The guidelines need to provide a framework that accommodates progress in the science of cancer risk assessment and establishes parameters for risk management decision-making (e.g., describe plausible options and preferred option; present multiple estimates of risk).

MODE OF ACTION

Considerable discussion focused on the implications of using mode of action for characterizing hazards and dose-response relationships. All reviewers endorsed the use of mode of action and provided several examples of its applicability (i.e., species to species extrapolation, tissue sensitivity and specificity, high to low extrapolation). Reviewers recommended that a statement be added to the preamble of the guidelines acknowledging the limitations on scientific inquiry for providing a complete understanding of the mode(s) of action by which any particular chemical causes cancer. The statement should make clear that when a reasonable knowledge of critical events in the mechanistic process based on high-quality research is available, such information should be used to produce a better risk assessment.

Figure 4-1 illustrates some probable modes of action (see section 4). The reviewers pointed out that although figure 4-1 does not provide an exhaustive list of modes of action, a significant number of chemicals and agents (e.g., radionuclides) would likely fit into the identified boxes. Moreover, a substance can have more than one mode of action, some of which might be identified by the boxes in figure 4-1. As knowledge of effects increases, there will be a need to incorporate these advances into the guidelines. To adequately characterize each mode of action, reviewers recommended that supplemental information be prepared both in the near term and as new information becomes available. Reviewers recommended that *mode of action* and *mechanism* be defined in the guidelines.

Another area of discussion was the mode of action as a determinant of the shape of the dose-response curve. Although mode of action cannot always be fully explained, reviewers believe that often sufficient information is available on which to base a reasonable understanding. All reviewers agreed that if the mode of action is not known, then a simple linear extrapolation default methodology can be used. Reviewers recommended providing examples of dose-response relationships for chemicals with genotoxic modes of action and examples of the relationship between mode of action and linear or nonlinear curves for nongenotoxic chemicals. They suggested that the weight of evidence judgment of mode of action will support developing a biologically based dose response model. Additionally, a framework for judging the adequacy of mode of action data should be established.

The mode of action breakout group also made several general recommendations, including:

- The nature and flow of the risk assessment process should reflect the role of hazard assessment as depicted in figure 4-2.
- The guidelines should address judging the quality of data other than animal studies (e.g., epidemiologic studies, short-term studies).
- The NAS' carcinogen classification system should be considered. Considerable thought has gone into the development of NAS' four categories. For example, category II allows both the risk assessor and risk manager to deal with limited conditions.
- Since cancer is a multifactorial process, an illustration or flow diagram of the cancer process should be provided in the guidelines.
- EPA should provide an explanation of the relationship of the new guidelines to the 1986 guidelines. Why are the guidelines being changed? Who is the intended audience? How will the guidelines be used?
- If guidance on the use of mode of action is to be provided in a meaningful way, then the role of expert opinion and peer review must be delineated. The guidelines must define a level of acceptance in terms of data quality in the scientific community and account for different levels of information.
- The guidelines should include a statement about supporting regulatory programs. The document also should acknowledge that a wide variety of risk assessments are performed, including those that do not include mode of action information.
- EPA should consider international harmonization of the guidelines.

- When the next draft of the guidelines is complete, EPA should conduct a workshop at which several chemicals are carried through the approach outlined in the guidelines.

- EPA should develop a process for communicating the hazard narrative to the public.

DEFAULT ASSUMPTIONS

All the expert reviewers agreed with the guidelines' recommended use of defaults in risk assessment. Defaults lead to consistency as well as accommodate some flexibility in risk assessments, especially when expedited decision-making is required. Defaults are useful when either available data are inadequate or to apply policy. Defaults can be science related, policy driven, or some combination.

Although reviewers were in general agreement about the use of defaults when sufficient data are not available, several reviewers cautioned that defaults should be used reluctantly; when possible, alternatives other than defaults should be investigated and a full scientific analysis provided. The risk characterization should include a narrative that lists the plausible alternatives and provides a clear summary of the risk assessor's level of confidence in each alternative, including the most likely alternative, if possible. The risk manager then will have sufficient information to make a policy decision about which alternative to use; however, the distinction between science- and policy-driven decisions should be explicitly recognized.

Although reviewers agreed with the NAS/NRC recommendation that EPA list, explain, and justify the use of defaults, they also expressed the opinion that EPA should not attempt to write an "encyclopedia" of defaults. Rather, the Agency should compile a list of the most frequently used defaults along with their explanation, so that risk assessors would not need to justify each default on a case-by-case basis. Reviewers also endorsed a separate process for reviewing changes in defaults (e.g., peer review). It also was recommended that EPA define *defaults* in the guidelines.

The default assumption breakout group spent considerable time discussing defaults that are frequently used but rarely recognized; for example:

- Humans have no variation among them in susceptibility.
- Chemicals have one mode of action.
- Chemicals act independently (i.e., interactions are not of consequence).
- The nature of an exposure (i.e., uptake, route) may be important.

Reviewers also discussed specific defaults:

- **Surface area.** Reviewers expressed differences of opinion on the justification of the cross-species default scaling factor. Some theoretical rationales support the 3/4 power. All reviewers, however, support use of pharmacokinetics, pharmacodynamics, or biomarker data to replace default assumptions. The guidelines need to clarify this issue.
- **Exposure metric.** Reviewers agreed with the 1994 *Federal Register* notice that lifetime average daily dose (LADD) is the appropriate default metric for exposure estimates.
- **Linear modeling.** The guidelines should indicate that the multistage model, not the linear multistage model, is being recommended to estimate ED_{10}s (effective doses). If the confidence region on the ED_{10} is of interest, however, other, more constrained models may be more appropriate (e.g., Weibull).
- **Cross species.** Some reviewers expressed the opinion that, in the absence of cross-species pharmacodynamic data, pharmacokinetic data cannot be used for cross-species extrapolation. Others would use pharmacokinetic data entirely for cross-species extrapolation without further adjustment, and still others would use pharmacokinetics adjustments but still use the 3/4 power as a pharmacodynamic factor. Cross-species extrapolation needs further explanation in the guidelines.

Recognizing that defaults should not be considered to be based on static assumptions, the group also addressed how defaults can be modified, changed, or replaced:

- More data can be acquired.
- Either more or less conservative changes in policy can be made.

No general pattern for how defaults will change can be discerned. Some reviewers suggest, however, that defaults may develop with a greater emphasis on reducing uncertainty (i.e., a better default may be one that lowers uncertainty). Reviewers recommended that in general and under specific circumstances, EPA should develop guidance for when defaults should be added or changed based on both science and policy. Moreover, EPA should clearly express the uncertainty associated with defaults in risk assessments. Reviewers also recommended that EPA conduct workshops for evaluating the use of defaults and alternatives for specific chemicals of concern.

DOSE RESPONSE

Members of the dose-response breakout group began their discussions by defining dose-response terms (e.g., biologically based models are models that have parameters, derived from biological measurements, that are independent of curve-fitting tumor data, and threshold models are a type of biologically based model). Reviewers recommended that EPA encourage the use of biological information by establishing incentives and a process for their incorporation. Reviewers recommended that the guidelines suggest on a case-by-case basis all plausible dose-response models. Discussion of each model should be accompanied by an explanation of the risk assessors confidence in each alternative, including the mostly likely alternative.

Reviewers recommended that when mechanistic data indicates that a threshold approach is appropriate, margin of exposure calculations are the appropriate measure for comparing animal exposure to human exposures. Additionally, qualitative descriptors of the degree of risk reduction for various margins of exposure should be discussed.

With few exceptions, for most data sets, ED_{10}, ED_{25}, the linear multistage (LMS) model, and models by Krewski and Gaylor-Kodell (see section 4) give approximately the same low-dose extrapolation. Reviewers generally agreed with EPA's use of the ED_{10} and a straightline extrapolation to the origin. Reviewers suggested that use of the LMS and other models is inappropriate for extrapolating risk from upper-bound confidence intervals and dose from lower-

bound confidence intervals. In some cases, however, extrapolating from the lowest effective dose rather than the ED_{10} may be more appropriate, especially when the pharmacokinetics are unknown.

Low-dose extrapolation models (i.e., nonlinear models) must reflect biological processes or, in the absence of data, be used as defaults (i.e., linear models). The concept of using generic nonlinear models to slightly extend the observed tumor dose response below the observed range was discussed among reviewers. Reviewers cautioned, however, that this approach should only be used if it is supported by extensive dose-response data.

Although biologically based models cannot be used for every risk assessment, occasionally they can be used to extrapolate below the ED_{10} by using surrogate measures of dose or response (e.g., biomarkers). In such cases, the lowest point of extrapolation should be the lowest point in the experimentally accessible range, and mode of action should be considered. Several reviewers suggested that the guidelines include an explanation of how a surrogate data set should be selected and how epidemiologic data can be used for estimating the ED_{10}.

Noting that biologically based models often can be fit to available data, reviewers discussed the relevance of estimated parameters to actual exposures under consideration. Reviewers recommended that a narrative on the certainties and uncertainties of the parameters and the model should be included in the assessment. Monte Carlo analyses was endorsed as an appropriate method to estimate the uncertainty and sensitivity in biologically based models. Reviewers also advised EPA to provide guidance on how to justify a decision against using a biologically based model. Suggested explanations included insufficient data and the model's possible inappropriateness for lower tiers of a tiered risk assessment.

Reviewers recommended that a simple definition of *margins of exposure* and guidance on their use be provided in the guidelines. In particular, reviewers suggested that the guidelines address whether uncertainty factors should be applied or whether they should be reported as part of the decision-making process when comparing margins of exposure to acceptable exposure levels. Reviews recommended the degree of risk reduction associated with the margin of exposure should be explained in the risk characterization section of the risk assessment, along with margin of exposure calculations, as factual benchmarks for reporting exposures. The recommendation also was

made that EPA discuss how other organizations (e.g., the State of California) incorporate interindividual variability into their risk assessments.

HAZARD IDENTIFICATION

Reviewers provided several recommendations on how to improve the hazard identification process:

- Expand the use and explanation of epidemiologic and other human data. Also, adopt a new default: High-quality negative epidemiologic data takes precedence over positive bioassay results if the plausible mechanism in animals is irrelevant to humans. Further, modify the meta-analysis explanation to include a descriptive analysis/assessment.

- Provide guidance on the criteria and process for evaluating the relevance of animal toxicity data to humans. For example, expand the discussion on maximum tolerated dose, and review the implications of using genetically modified strains in routine animal studies. Also, encourage consideration of the significance of spontaneous tumor sites on a case-by-case basis.

- For cases where only limited chronic toxicity data are available, recommend use of the results of validated short-term tests and other data (e.g., structure-activity relationship data) to provide preliminary classification of agents (i.e., for screening or creating incentives for the generation of new information). Encourage the use of expert judgment when considering the weight of evidence of mutagenicity data. Recommend assessing the significance of positive *in vivo* genotoxins.

- Describe a default procedure for prioritizing chemicals of concern on the basis of available non-chronic testing data (e.g., short-term bioassays).

- For cases where nonchronic testing data are limited, recommend addressing the relevance, sensitivity, and specificity of available genotoxicity tests and suggest an approach for incorporating pharmacokinetics data. Also, develop test methods for detecting other important modes of action.

- Describe how expedited hazard identification decisions will be integrated in a tiered risk assessment process with the more comprehensive hazard assessment process established by the draft guidelines.

Reviewers supported a one-step rather than a three-step hazard identification process, suggesting that equal consideration of all data at one time will improve the value of the assessment. EPA should explain how a one-step process will differ from the present approach.

All reviewers agreed that a narrative summary should be a primary component of the hazard identification. The narrative should provide a clear and concise description of the strengths and weaknesses of the assessment.

Considerable discussion took place on the issue of classification. Some reviewers contended that only a hazard narrative was needed to summarize available information on carcinogenic risk to humans; others held that numerical descriptors are essential. Ultimately the hazard identification breakout group agreed on the need for some type of abbreviated classification scheme that would incorporate weight of evidence, exposure conditions, and relevance to humans. The group suggested that at least four categories be used, rather than the three broad categories proposed in the draft guidelines. Reviewers recommended that the four categories presented in the NRC report *Science and Judgment in Risk Assessment* (see Section 4) be modified to include information on weight of evidence and incorporated into the draft guidelines.

SECTION THREE

CHAIRPERSON'S SUMMARY OF THE WORKSHOP

Ronald Wyzga
Health Studies Program
Electric Power Research Institute
Palo Alto, California

EPA has undertaken an extensive effort to update the 1986 *Cancer Risk Assessment Guidelines*, as reflected by the recently issued draft revisions. The revisions would broaden the risk assessment process to include evidence apart from tumor effects, information about route of exposure and mode of action, and more than one default mode to allow various alternative situations to be recognized and considered. Additionally, the revised guidelines would recognize the growing interest in risk characterization as a part of the process.

Rather than focusing the workshop on the development of a consensus concerning the revised guidelines, EPA sought to identify key issues in need of further consideration in the guidelines development process. Four subject-specific categories were suggested as a means of organizing the issues raised:

- mode of action;
- default assumptions;
- dose response; and
- hazard identification.

With these topic areas providing a general framework for discussion, workshop participants were asked to address a series of specific questions raised in the Charge to Workshop Reviewers (see Appendix B) regarding the draft revisions. Participants also were encouraged to discuss other aspects of the guidelines related to those raised by the list of questions.

The workshop discussions yielded comments concerning aspects of the guidelines that would benefit from further consideration as well as specific recommendations for enhancing the draft revisions. Not all proposed changes were based on a consensus; thus, dissention within the workshop concerning particular suggestions is noted (see section 2).

In discussions among the workshop's expert reviewers, several broad, recurring themes emerged. These include:

- **Use of the guidelines.** Greater knowledge/more discussion about use of the guidelines would facilitate a more thorough evaluation, since the community of users is broader than originally imagined. Different uses of risk assessment require different levels of detail; hence, risk assessment guidelines that support assessments of differing detail would better serve the user community. A greater understanding of the use of assessments would particularly facilitate providing better guidance in the risk characterization section of the guidelines. Some users would find it especially helpful to have more guidance on how to consider exposure in risk assessments; others might want specific information for different population subgroups.
- **Accessibility of guidelines.** Simplicity is a virtue in regard to the guidelines, and they should not be more complicated than necessary. The immediacy and accessibility of the guidelines would facilitate their use and communication among potential users. Such an emphasis would be consistent with a tiered approach to risk assessment, with less-sophisticated assessments satisfying particular needs. In addition, simpler concepts are easier to understand, and greater understanding can facilitate wider acceptance.
- **Use of scientific information.** Although all available scientific information should be considered when assessing risk, all of the information does not need to be incorporated into the ultimate assessment. Some disagreement among workshop participants concerned what and how much information should be incorporated; hence, differences of opinion largely concerned details relating to specific risk assessments.
- **Use of scientific judgment.** Risk assessment must incorporate the judgments/ opinions of experts; yet the extent to which these can be codified is limited. Indeed, guidance cannot be designed to cover all potential risk assessments. Data availability and interpretation will differ greatly for various agents, and all circumstances cannot be foreseen or addressed a priori. Judgments will have to be made about the treatment of information for specific risk assessments.

- **Risk communication.** Scientists must be willing to make judgments and express opinions about scientific data, models, and phenomena, rather than deferring to risk managers. These expert opinions/judgments must be adequately communicated to risk managers. Thus the guidelines should promote interaction between experts and risk managers and encourage risk managers to provide feedback on the adequacy of risk assessments.

- **Peer review.** Peer review should be a critical element in EPA's risk assessment process. Scientific judgments/opinions should reflect those of the scientific community. Peer review is particularly important because it can lead to the availability of additional information, resulting in more thorough risk assessments.

- **Use of case studies and workshops.** Review of the guidelines would be facilitated by developing case studies that follow the recommended assessment protocol. It is difficult to fully understand the implementation and the implications of the revised guidelines by examining them only in the abstract. Case studies using research data would illustrate the use of the guidelines and elucidate problems associated with their implementation. Workshops for reviewing these case studies along with the guidelines would be particularly valuable.

- **Development of supplemental materials.** The more elaboration/discussion concerning risk assessment methods, the better. Thus, the development of supplemental materials (e.g., EPA's "purple books") is desirable. Specific interpretations/uses of information will warrant additional discussion/elaboration for the risk assessment and management communities. Supplemental volumes also would present an opportunity to describe and rationalize the use of specific practices/methodologies.

- **Linking assessment components and risk-related guidance.** Although the workshop emphasized particular issues and components of risk assessment, the various components are interrelated in a way that is not unidirectional. Interaction among the various components must be articulated more fully. Discussion of the linkages between these guidelines and guidance for exposure assessment and combinations of the two also would be desirable.

- **Recognition of scientific progress.** Risk assessment guidelines must explicitly recognize scientific progress and make provision for updating risk assessment methods. Risk assessments should not be postponed until all data are available, however, since risk assessment is an iterative process that continues over the long term. Thus, there is a need to perform risk assessments in a timely manner using available information, and there is a need to alter/update risk assessments when more information becomes available.

- **Endorsement of the guidelines revision effort.** In general, workshop participants expressed the opinion that the revised draft guidelines represent an improvement over the 1986 guidelines. Although the expert reviewers applauded EPA's efforts to revise the guidelines, they did not endorse each specific revision. Rather, they made several suggestions for improving the proposed revisions or for giving particular revisions further consideration. These suggestions are provided elsewhere in this report (see sections 2 and 4).

SECTION FOUR

BREAKOUT GROUP SUMMARIES

Mode of Action Breakout Group

Carol Henry, Chair
Office of Integrated Risk Management
U.S. Department of Energy
Washington, DC

Henry Andersen
Bureau of Public Health
Madison, WI

Clay Frederick
Rohm & Haas Company
Spring House, PA

James Swenberg
Curriculum in Toxicology
University of North Carolina
Chapel Hill, NC

J. Carl Barrett
Environmental Carcinogenesis Program
National Institute for Environmental Health Sciences
Research Triangle Park, NC

Tore Sanner
Institute for Cancer Research
The Norwegian Radium Hospital
Oslo, Norway

Ronald Wyzga
Health Studies Program
Electric Power Research Institute
Palo Alto, CA

THE ROLE OF MODE OF ACTION IN RISK ASSESSMENTS

Although the use of mechanistic data in risk assessment has long been recognized as desirable, available data rarely demonstrate carcinogenic processes with any certainty. Indeed, the 1986 cancer guidelines called for the evaluation of relevant information, but to date risk assessments seldom have made full use of available information, even when information might be sufficient to indicate a general mode of action.

In the past, most risk assessments have relied heavily on animal tumor data from carcinogenicity bioassays run at high doses to mathematically extrapolate potential risks to humans at much lower exposures. In some instances, this process was further complicated by, for example, different routes and durations of exposure. Thus, such risk assessments are plagued with a large degree of uncertainty. The proposed revised guidelines for cancer risk assessment emphasize the inclusion of more biologically based data as a means to reduce some of the uncertainty associated with the extrapolation of risk. A major focus of this biological data is the probable mode of action that leads to the inducement of cancer.

The workshop participants commended EPA for this emphasis in the revised guidelines and for recognizing that understanding and utilizing data on the probable mode(s) of action is critical for developing better assessments of cancer risk. While participants recognized that the mechanism(s) by which any chemical causes cancer may never be completely understood, they agreed that this should not preclude the incorporation of mode of action data into the risk assessment process when reasonable scientific studies support the data.

It is likely that multiple modes of action may be involved in the inducement of neoplasia by individual chemicals. Probable modes of action that need to be considered are shown in figure 4-1. When one or more modes of action can be shown to be causally involved in the carcinogenic process, data on this (these) endpoint should be factored into the risk assessment.

For a large number of agents (including both chemicals and radionuclides), direct mutagenic effects have been causally associated with critical events in carcinogenesis (e.g., aflatoxin). Similarly, there are numerous examples of agents that cause increases in cell proliferation and therefore increase the probability of enhanced spontaneous mutagenesis and clonal expansion (e.g., d-limonene, sulfamethazine). Other agents can induce indirect mutagenic effects by affecting tubulin assembly/disassembly and causing or inducing numerical aberrations in chromosomes (e.g. vinblastine), or by inhibiting DNA repair (e.g., arsenic, Marcus and Rispin, 1988). Although less information is available on heritable epigenetic events (e.g., alterations in DNA methylation), such events constitute a likely mode of action. Clonal expansion also can occur by inhibiting the rate of cell death in initiated cell populations. It is expected that additional modes of action that are

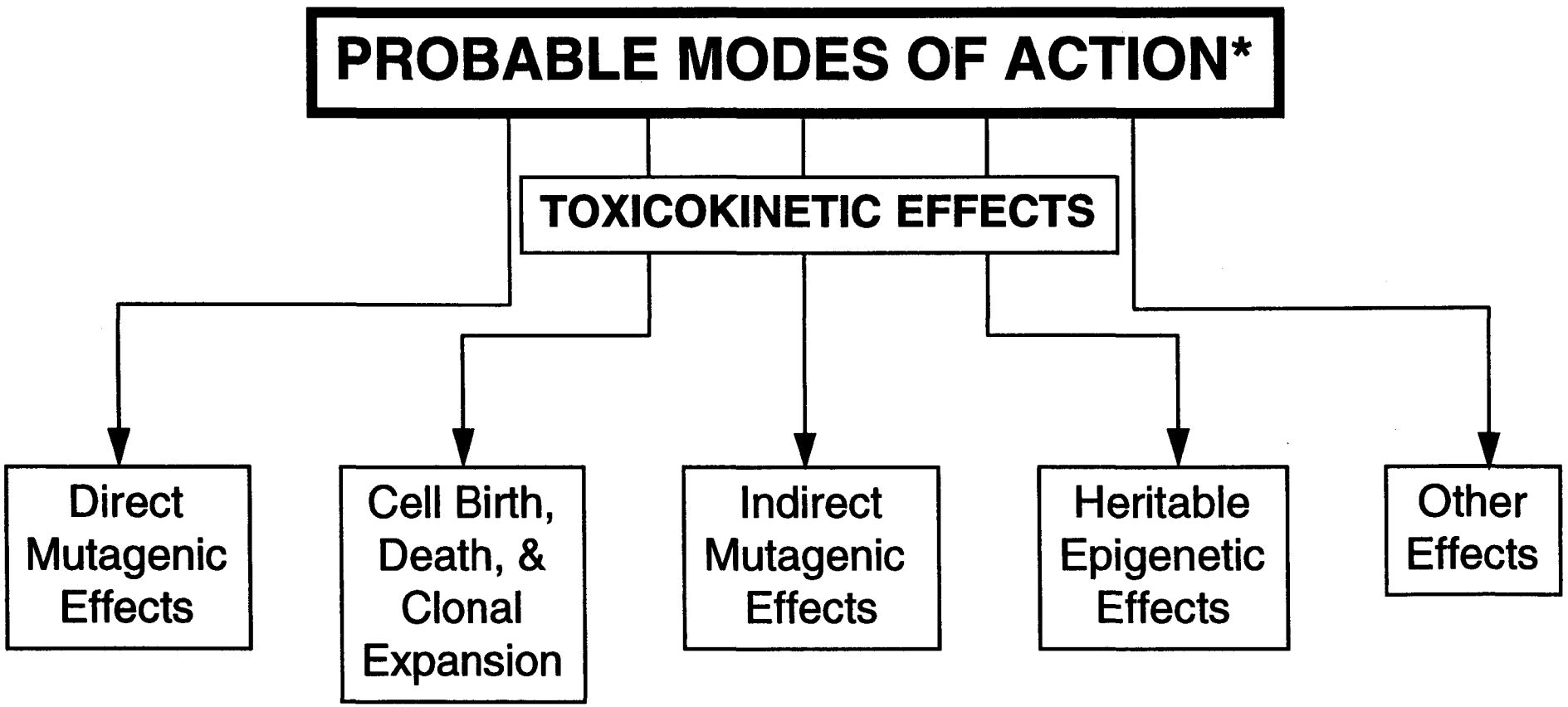

Figure 4-1. Probable modes of action involved in the carcinogenic process.

unknown at present will be equally important (e.g., mode[s] of action of chemical mixtures or mixtures of chemicals and radionuclides).

Formaldehyde represents an example of a compound for which multiple modes of action affect the carcinogenic process. Although this compound is a direct mutagen, the dose that reaches the DNA is affected by detoxication, a process that becomes saturated at high exposures. Therefore, a nonlinear molecular dose response occurs. Cell proliferation also is increased at high concentrations, leading to increased mutations and increased clonal expansion at high doses. All of such information is relevant to a better assessment of cancer risk. Types of data that need to be considered in the hazard identification section of the guidelines include: evidence of saturation of metabolic activation, detoxication, and DNA repair; dose-related effects on cell proliferation, apoptosis, and clonal expansion; effects on cytoskeletal proteins involved with mitosis; alterations in expression of critical genes.

MODE OF ACTION AS A DETERMINANT OF THE SHAPE OF THE DOSE-RESPONSE CURVE

To facilitate the incorporation of information on mode of action into risk assessments, supplementary documents (e.g., EPA's "purple books") should be developed to describe the state of the science in the appropriate areas. Structured in this way, the guidelines would accommodate the evolution of the science in cancer biology.

Notwithstanding the limitations on our understanding of the mechanism(s) by which any chemical causes cancer, it is important that information for which there is a high level of confidence be used to produce better risk assessments. Such information should be supported by a reasonable understanding of the critical events in the cancer-causing process and be based on high-quality research. In the absence of mode of action data, this breakout group would support use of a simple linear extrapolation default methodology.

Generally, compounds that are classically described as genotoxic (i.e., positive in standard genotoxicity assays and generally known to induce tumors in multiple tissues in chronic rodent bioassays) are expected to be linear in the non-observed range (i.e., linear dose response at very low

doses). Well-documented examples are the rodent liver tumor responses following dietary exposure to 2-acetyl- aminofluorene (AAF), (ED_{01} study; Cohen and Ellwein, 1990) or aflatoxin B_1. The slope and the shape of the dose-response curve of a genotoxic compound, however, may be influenced by other factors (e.g., the nonlinear response for the inducement of bladder tumors in the ED_{01} study that has been attributed to the increased rate of cell proliferation in the bladder epithelium induced by high doses of AAF).

Compounds that are not positive in a standard battery of genotoxicity tests may have either a linear or nonlinear carcinogenic dose response. Justification of a nonlinear dose response is dependent on (1) the weight of evidence supporting a lack of genotoxicity, and (2) scientific data sufficient to support a mode of action that involves a nonlinear dose response. Some examples of modes of action that may exhibit a nonlinear carcinogenic dose response include:

- stimulation of an increase in the cell proliferation rate of a sensitive tissue (e.g., BHA inducement of rodent forestomach tumors at high-dose levels, phorbol ester induction of mouse skin tumors following dermal application, saccharin induction of rat bladder tumors at high dose levels);
- interaction with the proteins of the cytoskeleton or with proteins involved in cell division (e.g., vincristine inhibition of tubulin assembly and etoposide inhibition of topoisomerase II);
- the sustained induction of compensatory cell replication in a sensitive tissue associated with cytotoxicity (e.g., gavage dosing of chloroform and induction of rodent liver tumors); and
- peroxisome proliferation and the induction of rodent liver tumors (e.g., clofibrate).

Indirect mechanisms of genotoxicity (which may serve as initiating events for carcinogenicity) have recently been reviewed by an international commission (ICPEMC, 1991).

EPA should consider what constitutes adequacy of information to support the use of mode of action data. Questions that should be addressed include:

- Has a scientific data base been generated to describe a mode of action to explain the formation of tumors in the human epidemiology study or in the animal bioassay?

- Is the mode of action concept consistent with the generally accepted understanding of the mechanisms of carcinogenesis?
- Has the science describing the mode of action concept been subjected to substantive peer review and been published?
- Is there information to suggest that the mode of action for tumor inducement can, or cannot, occur in humans (or at least upper primates)?

GENERAL RECOMMENDATIONS

The guidelines document needs to place greater emphasis on the critical role mode of action plays in determining both human hazard and potential dose-response patterns. A recommended approach is presented in figure 4-2.

The *preamble* to the guidelines should include information on the nature and flow of the entire risk assessment process (figure 4-2). It should also include the four elements of the NAS paradigm (i.e., hazard, dose response, exposure assessment, and risk characterization). Additionally, the document should describe the modification made to the *hazard assessment* in the proposal to, for example, place more emphasis on biological information other than tumor data as well as other inputs (e.g., physicochemical and structure-activity relationship [SAR] information). This information is than analyzed along with the tumor information to yield:

- mode(s) of carcinogenic action;
- conditions of hazard (i.e., exposure route and pattern/magnitude);
- guidance for dose response;
- hazard characterization, which includes:
  - a general summary of hazard cases
  - a classification of descriptor(s) using the NRC scheme
  - a narrative

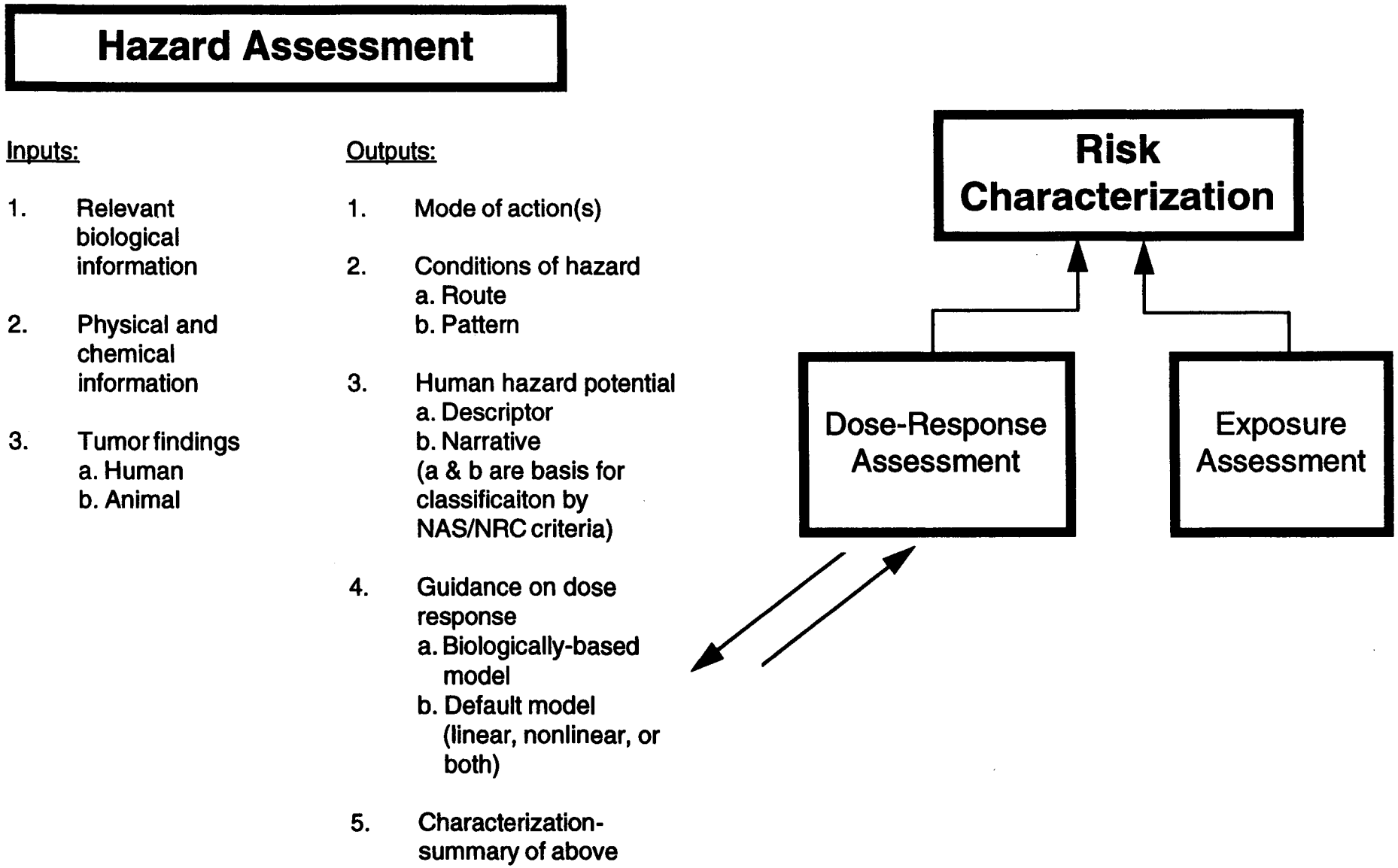

Figure 4-2. Role of modes of action in risk assessment process.

In departing from the 1986 guidelines for the classification scheme, EPA should use the categories in the NRC document *Science and Judgement* (presented in table 4-1).

To conduct *dose-response assessments*, elements from the hazard assessment (e.g., mode of action, conditions of hazard, and guidance on dose response) are used to project concerns for route-to-route, high-to-low, and species-to-species extrapolation. Generally, biologically based dose-response models are used when data and biological understanding allows. In the absence of such information, one of two defaults or both are considered:

- linear
- margin of exposure

Exposure assessment describes the expected human exposure. The exposure values are melded with dose-response assessment information to project potential concerns about human exposures (in the last section of the assessment, risk characterization). In the opinion of the breakout group, both the exposure assessment and the risk characterization sections of the draft guidelines need to be further developed.

INTERNATIONAL COORDINATION

One of the goals in the Agenda 21 that was agreed on at the Rio-Conference in June 1992 was to harmonize classification systems for chemicals. The Organization of Economic Cooperation and Development (OECD) will play an important role in this work; at the 20th Joint Meeting of OECD in May 1993, it was decided that Norway and the Netherlands should act as lead countries for work on the endpoint carcinogenicity. For a number of reasons, international harmonization of quantitative risk assessment is not currently practical. Nevertheless, as EPA revises its guidelines, these international efforts need to be acknowledged and accommodated to the extent possible.

Table 4-1

NRC CARCINOGENICITY CLASSIFICATION SCHEME

Category	Nature of Evidence
Category I Might pose a carcinogenic hazard to humans under any conditions of exposure. Magnitude of risk depends on dose-response relationship and extent of human exposure.	■ Evidence of carcinogenicity in either human or animal studies (strength of evidence varies; see Step 2 [see source]). ■ No information available to raise doubts about the relevance to humans of animal model or results. ■ No information available to raise doubts about relevance of conditions of exposure (route, dose, timing, duration, etc.) under which carcinogenic effects were observed to conditions of exposure likely to be experienced by human populations exposed environmentally.
Category II Might pose a carcinogenic hazard to humans, but only under limited conditions. Whether a risk exists in specific circumstances depends on whether those conditions exist. Dose-response and exposure assessments must be completed to identify conditions under which risk exists.	■ Evidence of carcinogenicity in either human or animal studies (strength of evidence varies; see Step 2). ■ Scientific information available to show that there are *limitations* in the conditions under which carcinogenicity might be expressed, owing to questions about the relevance to humans of the animal models or results or relevance of the conditions of exposure (route, dose, timing, duration, etc.) under which carcinogenic effects were observed to conditions of exposure likely to be experienced by human populations exposed environmentally.
Category III Notwithstanding the evidence of carcinogenicity in animals, not likely to pose a carcinogenic hazard to humans under any conditions.	■ Evidence of carcinogenicity in animal studies. ■ Scientific information available to show that the animal models or results are not relevant to humans under any conditions.
Category IV Evidence available to demonstrate lack of carcinogenicity or no evidence available.	■ No evidence of carcinogenicity or evidence of noncarcinogenicity (weight of negative evidence varies; see Step 2).

Source: Committee on Risk Assessment of Hazardous Air Pollutants, 1994.

SPECIFIC RECOMMENDATIONS

Relationship of the Proposed New Guidelines to the 1986 Guidelines

A clear explanation of the practical differences between the earlier guidelines and the proposed revision must be provided both for the scientific community and the public. From the public's perspective, despite the move to being less methodologically prescriptive, the guidelines need to retain their principle underlying public health philosophy: that EPA carcinogen risk assessment conclusions should be "conservative to public health." This probably needs to be stated in the beginning of the document. Further, the document needs to state who the intended audience is as well as what types of decisions these guidelines are intended to support.

The Role of Expert Opinion in the Proposed New Guidelines

The proposed guidelines recommend continuing the process of translating "expert opinion" into objective components, which allows the decision processes to be described and justified so that they are better understood. The assessment decision regarding mode of action will require considerable use of expert judgment. Peer review and public review will need to be a critical element in deciding about the robustness of the mode of action evaluation and the credibility of the scientific judgments.

Support for Regulatory Programs

It is important to stress that not all carcinogen risk assessments will be as comprehensive as outlined in the guidelines. In the preamble, EPA should acknowledge in more detail the variety of needs for assessing cancer risk for various regulatory programs and the appropriateness of expedited and comprehensive risk assessments. This has implications for the commitment of a sufficient level of effort and adequate resources for the risk assessment.

The Proposed New Guidelines and the Case Studies

EPA should consider holding a workshop to demonstrate how the proposed guidelines would be used for specific case studies (including both expedited and comprehensive risk assessments).

Visual Representation of Information

To the extent possible, EPA should provide visual guidance in the form of illustrations or flow charts to enhance understanding of the guidelines themselves as well as the complex biological systems considered (e.g., a diagram to represent the multifactorial components of carcinogenesis).

Uncertainty Characterization

Additional information should be included to address the issue of uncertainty with regard to the selection of the mode of action, causality, the appropriate statistical treatment of dose-response models, and the additivity of effect or exposure within a mode of action or across modes of action.

REFERENCES

Committee on Risk Assessment of Hazardous Air Pollutants (1994) Science and judgment in risk assessment. Washington, DC: National Academy Press, pp. 7-23.

Cohen, S.M.; Ellwein, L.B. (1990) Proliferative and genotoxic cellular effects in 2-acetylaminofluorene bladder and liver carcinogenesis: biological modeling of the ED_{01} study. Toxicol. Appl. Pharmacol. 104:79-93.

International Commission for Protection Against Environmental Mutagens and Carcinogens (ICPEMC) (1991) Genotoxicity under extreme culture conditions. Mutation Res. 257: 145 et seq.

Marcus, W.L.; Rispin, A.S. (1988) Threshold carcinogenicity using arsenic as an example. In: Cothern, C.R.; Mehlman, M.A.; Marcus, W.L., eds. Risk assessment and risk management of industrial and environmental chemicals. Princeton, NJ: Princeton Scientific Publishing, pp. 133-158.

Default Assumptions Breakout Group

Marvin Schneiderman, Chair
National Research Council
National Academy of Science
Washington, DC

Kim Hooper
Hazardous Materials Laboratory
California Environmental
Protection Agency
Berkeley, CA

Peter Shields
Laboratory of Human Carcinogenesis
National Cancer Institute
Bethesda, MD

James Wilson
Regulatory Affairs
Monsanto Company
St. Louis, MO

John Moore
Institute for Evaluating Health Risks
Washington, DC

Leslie Stayner
Division of Standards Development and
Technology Transfer
National Institute for Occupational
Safety and Health
Cincinnati, OH

SPECIFYING DEFAULT ASSUMPTIONS

"Default" is the descriptive label attached to the reasonable replacements of the scientific information needed for integration into risk assessments when the actual data are either incomplete, inadequate or unavailable. A limited number of policy-driven defaults also may need to be entered into the risk assessment process to respond to, or achieve, desired policy goals. Because defaults are important for facilitating expedited risk assessments, EPA should be as explicit as possible about default procedures so that they can be easily incorporated into the process.

Default assumptions are essential to almost all EPA programs, particularly those tiered programs that identify exposure to cancer-causing agents and attempt to estimate the consequences of these exposures. The rigor associated with such determinations will vary, ranging from the simple data used first in a tiered approach to data of increasing quantity and complexity that are required

in the higher tiers. Usually, decisions arising from the higher tiers, which typically involve more data and fewer defaults, are expected to remain in effect for a longer time.

Frequently, the lowest tiers will draw only upon limited amounts of data, necessitating the use of several default assumptions. The defaults used in the lowest tiers relate to decisions about which components of an assessment are characterized by incomplete or hard-to-develop scientific knowledge. As a policy matter, the use of such defaults will lead to a decision or standard that should be highly protective of the public health. Since defaults usually are derived from incomplete knowledge, however, they impart varying degrees of uncertainty regarding estimates of the carcinogenicity or potency of a particular agent. When an agent is subjected to a higher-tiered risk assessment (i.e., an assessment that is expected to remain operative for a long time), the availability and use of more robust data may supplant, or at least modify, many of the default assumptions. In such cases there is a commensurate decrease in the uncertainty associated with the estimates of risk and the subsequent regulatory standards established.

Thus it is strongly recommended that EPA provide a list and accompanying evaluations of the most important or most frequently used default assumptions factored into risk assessments. This list, which should be peer reviewed by a multidisciplinary panel of experts, should include:

- description of the defaults;
- identification of the components of the defaults arising largely out of science considerations in contrast to those derived largely from policy considerations;
- justification for using the defaults;
- enumeration of limitations of the defaults;
- explanation of how the defaults affect the risk assessment;
- description of the types of data and how much data would be needed to modify the defaults to reduce uncertainty; and
- description of the types of data and how much data would justify not using the defaults or would lead to more plausible defaults or methods (e.g., molecular genetic studies).

A definitive version of such a list would need to be created so that particular defaults would not need to be justified each time a risk assessment is conducted. Nonetheless, the use of the defaults would still need to be considered on a case-by-case basis in regard to the available data to determine if the default should be utilized or modified. Also, assumptions not on the list will need to be justified when factored into a risk assessment.

The list should include both stated assumptions and significant previously unstated assumptions.

Stated assumptions:

- Laboratory animal studies are predictive of human risk.
- Existing laboratory methodologies and models allow for low-dose extrapolation.
- The maximally tolerated dose (MTD) used in laboratory animal models is appropriate for identifying probable human carcinogens or for determining that a material is not likely to be a carcinogen.
- Using body weight of a 3/4 scaling factor is the most appropriate method for converting equivalent dose from one species to another.
- The upper-bound estimate of risk is appropriate for establishing an acceptable dose for risk to humans.

Unstated assumptions:

- The human population is homogenous; susceptibilities within a population do not differ (e.g., by age, gender, genetics).
- Background exposures do not occur (i.e., exposures to other agents do not also contribute to the carcinogenic process in humans).
- Background cancers do not occur.

- Interactions (e.g., synergism, antagonism) among multiple agent exposures do not occur (or are only additive).

- Agents are either genotoxic or nongenotoxic, and these qualities determine the shape of extrapolation curves appropriate for human risk assessment.

Some further complications also should be considered. For example, default assumptions are a mixture of science and policy. Thus, there is a danger that the single numbers that are generally derived from these default methods may be interpreted by the public as representing actual levels of risk rather than expedient benchmarks for the purpose of risk management decision-making by EPA. For this reason, default procedures need to be replaced by procedures that fully utilize available scientific information and facilitate exploring the effect of alternative assumptions (i.e., sensitivity analyses) when possible.

Additionally, examining specific defaults along with the modification of risk assessments that might result from using different but related defaults may provide benefits in certain situations. Similarly, examining alternatives to existing default assumptions and quantitating the impact of these alternatives on the estimation of risk present clear benefits. Such sensitivity analyses can provide risk managers (and the public) with a greater understanding of the uncertainties underlying risk estimates. When possible, the risk assessor should provide information about which of the alternative assumptions appear to be most plausible. It should be clearly recognized in the guidelines, however, that such scientifically intensive analyses cannot always be performed, largely for pragmatic reasons.

MODIFYING DEFAULT ASSUMPTIONS

In certain situations, the "modifying" of defaults is appropriate. Thus, in any particular assessment, it may be appropriate to use scenario- or compound-specific information instead of a default. At times it also may be appropriate for EPA to consider replacing a default assumption with a different one.

Scenario-specific modifications. In general, defaults are modified when specific information implies that use of the default will give the "wrong answer"—that is, the implied regulatory decision will have unacceptable consequences. The consequences of a "wrong answer" can concern public health or economics, for example, as when information suggesting that humans are unusually susceptible to a substance would imply that the interspecies extrapolation default should be modified to protect public health. Usually, if decisions made using defaults do not imply unacceptable consequences, there is little reason to develop information needed to modify defaults.

The degree to which specific information should be used to modify a default depends primarily on the confidence that the analyst places in the reliability of the information. Thus highly reliable information should strongly modify defaults; information judged not to be so reliable should modify defaults weakly, if at all. In general, reliability is inferred from acceptance of the specific information by the scientific community doing research in relevant subject areas (i.e., the true peer group). Experience has shown that information from hypotheses that are novel or based on cutting-edge science are more slowly accepted as reliable by the peer community. EPA, however, should develop techniques for staying informed about the developing acceptance of new science, and should develop peer review approaches for early consideration of novel research.

Some defaults are currently considered to be dichotomous, allowing, for example, either one model or another to be used to infer a dose-response function. Well-tested techniques are available for converting these apparently dichotomous choices into continuous ones. Techniques for identifying the relative reliability of these choices and displaying the consequences of each are being explored. EPA should further the development of such techniques.

Adopting new defaults. In cases where the scientific basis for a default assumption has undergone significant recent evolution, EPA should seek to determine whether the scientific community accepts the developments. If it does, then EPA should adopt the value or other representation of the default that best satisfies the Agency's decision-making needs.

Dose-Response Breakout Group

Colin Park, Chair
Health and Environmental Sciences
The Dow Chemical Company
Midland, Michigan

Harvey Clewell
ICF/Kaiser International
Ruston, LA

Murray Cohn
U.S. Consumer Product Safety Commission
Bethesda, MD

Jay Goodman
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, MI

Thomas Starr
ENVIRON International Corporation
Raleigh, NC

The dose-response breakout group supported the emphasis in the revised guidelines on mode of action, thresholds, biological models, and biomarkers.

DEFINITION OF BIOLOGICALLY BASED MODELS

Biologically based models are models with parameters that are calculated independently of the mere curve fitting of tumor data. The issue in regard to the use of these models, concerns the relevance of the estimated parameters to the exposures being considered. Threshold models represent one class of biologically based models.

ED_{10} AS A STARTING POINT FOR LINEAR EXTRAPOLATION

The ED_{10} is defined as the effective dose corresponding to 10 percent extra risk, adjusting for background incidence using Abbott's correction. For most data sets, ED_{10}, ED_{25}, LMS, Krewski et al. (1984), Gaylor-Kodell (1980), and other models and methods provide approximately the same

low-dose extrapolations, and the estimates of ED_{10} are similar across models. For certain data sets with extreme curvature, however, shorter than two-fold differences between the methods may occur.

In general, breakout group members supported EPA in the use of the ED_{10} as an extrapolation point when substituting for the use of the LMS model for extrapolation. Group members felt that use of the LMS model, and other models for extrapolating risk from upper-bound confidence intervals or dose from lower-bound confidence intervals, are not generally appropriate.

The group also noted that extrapolating from the lowest dose at which a significant response was reported, rather than from the ED_{10}, may be more appropriate in some cases. ED_{10} is useful for achieving consistency when interpreting margins of exposure for human exposure, but the dose may not serve as the best starting point for some data sets. The lowest significant response data point might be better.

NONLINEAR MODELS

Low-dose extrapolation models must reflect biological processes. In general, curve-fitting at low doses for extrapolating animal or epidemiological data with no biological interpretation is not useful for regulatory purposes. In some cases, however, generic nonlinear models might be appropriately used to extend the observed tumor dose response somewhat below the observed range, but only when the model is supported by rich dose-response data, and even then with great caution.

ADVICE ON THE USE OF THRESHOLD MODELS

EPA has acknowledged the existence of thresholds for some compounds. Even though mechanistic data will never be perfect, in some instances application of threshold approaches will be appropriate. In such instances, linear extrapolation methods should not be used.

For threshold situations, margin of exposure calculations are the appropriate measure for comparison to human exposures. In these cases, qualitative descriptors of the degree of risk reduction for various margins of exposure should be discussed.

MARGINS OF EXPOSURE

Margins of exposure need to be more clearly defined and their use needs to be better explained. It should be made clear that the margins will be reported simply as statements of fact, with no indications made concerning the mechanism of action (e.g., thresholds).

For cases in which only margins of exposure are reported (i.e., no linear extrapolation is performed [ED_{10}/uncertainty factor (UF)]) and no biologically based model is reported), the analysis needs to include a narrative assessment about the likely degree of risk reduction associated with those margins of exposure (e.g., qualitative discussion of the steepness of the expected dose response below the ED_{10}, and the extent to which nonlinearities may exist).

BIOLOGICALLY BASED MODELS (USE OF NONTUMOR DATA)

Data that are drawn from experimentation beyond the tumor dose-response information (e.g., physiologically based pharmacokinetic [PBPK] models), as well as from modeling based on the data, can sometimes be used to extrapolate below the ED_{10} by using surrogate measures of dose or response to model the dose-response curve. Thus the lowest point of extrapolation should be the lowest point in the experimentally accessible region, which may be below the region where tumor responses are observed.

If human exposures are even lower than that final extrapolation value, then further extrapolation must start from that value by estimating the modeled risk at that point (i.e., the ED_{xx}). Extrapolation from that point uses the options discussed above (e.g., fractions of the ED_{xx}, margin of exposure).

SUFFICIENCY OF DATA TO FIT A BIOLOGICALLY BASED MODEL

Biologically based models often can be fit to the available data. In such cases, however, a narrative description of the certainty and relevance of the parameters and the model for the exposure scenario under consideration must be provided for the risk manager. Sometimes these models may be only qualitatively useful, since they may only indicate a likelihood of reduced risk. In other cases, however, they may be quantitative.

EPA should justify *not* using a biologically based model, even though there may be a simple justification; for example, available data may be insufficient or, for tiered risk assessments, biologically based models may not be appropriate for "lower" tiers. Additionally, certainty and uncertainty factors in the model(s) need to be discussed carefully in a narrative summary. Monte Carlo methods can be used to estimate uncertainty and sensitivity in biologically based and other models. Monte Carlo methods should be more fully used to quantify dose and exposure uncertainties.

USE OF ESTIMATED RISK VALUES

The majority of risk assessment specialists apparently believe that statistical risk models should not be used to calculate cancer prevalence in a population; rather, they believe that distributions of individual risk and numbers of individuals at risk should be reported separately.

TIERED RISK ASSESSMENTS

Tiered risk assessments are appropriate for use in the regulatory process. The degree of effort and sophistication of an assessment depends on the risk level anticipated and the value of a more detailed assessment. Simple risk assessments conducted to screen exposure scenarios are appropriate and will often use conservative default methodology. These assessments should be qualified, however, to the extent that they are explained as screening assessments only and do not

reflect the full range of available data. In these situations, use of biologically based models may not be warranted because of the degree of anticipated exposure or because of the cost of the effort.

AVERAGING TIME

LADD is generally appropriate for carcinogens; however, for margin of exposure calculations, guidance on the impact of the time factor is needed. Such guidance would likely be applicable on a case-by-case basis, depending on the likely human exposure scenarios and the animal data.

RISK CHARACTERIZATION

Maximum tolerated dose and tumor type. MTD issues (e.g., is the high dose used in the bioassay excessive and therefore not appropriate for risk assessment) and significance of tumor response (e.g., the mouse liver tumors, which are of questionable significance regarding human risk assessment) need to be discussed in the risk characterization section of an assessment, since not all tumor types are equal. This type of information should be discussed as a qualitative issue in the narrative summary. Relevance to humans is the important issue, and it needs to be given more prominence in the document in terms of guidance on risk characterization.

Margin of exposure calculations. Margin of exposure calculations should be included in all risk characterizations as factual benchmarks for reporting the magnitude of the difference between anticipated human exposures and the ED_{10} (or lowest significant tumor response level). Reporting a margin of exposure does not imply any particular mode of action nor any extrapolation procedures.

Dose-response alternatives. The technical part of an assessment should list plausible alternatives for dose-response models, and then present a clear summary of the level of confidence in each alternative, including the most likely alternative, if possible. The risk manager then will be able to make a policy choice.

Sielkin approach. The Sielkin approach for presenting distributions of uncertainty may be useful as a characterization and communication tool.

RESPONSE TO SPECIFIC QUESTIONS

Question 3(a). How and whether biologically based models can be applied generically in risk assessments, or can decisions only be approached on a case-by-case basis? What guidance might be given as to when and how to apply them?

Rhetorical question: case-by-case only.

For important risk assessments, if biological models can be fit, they can be useful in furthering the science, generating hypotheses, and focusing future research. This in itself is a useful outcome. Whether the models can be used to actually develop regulations can only be determined on a case-by-case basis.

Question 3(b). Whether it is rational today to use the three stated default methods for dose response extrapolation or other methods and illustrations given to assessors in the draft so that they can ably select default dose extrapolation procedures.

This has been dealt with by defining away the nonlinear model (i.e., there is only one default). Additionally, the margin of exposure calculation, as described above, should always be presented in the risk characterization as a reference point.

Question 3(c). The adequacy of the information and illustrations given to assessors in the draft so that they can ably select default dose extrapolation procedures.

The guidelines contain insufficient guidance. The breakout group encourages development of such supplemental guidance documents (e.g., EPA's"purple books"). Real examples are needed. The group recognized that EPA can never issue guidelines on a "cookbook basis," but advocated the development of additional guidance and illustrative material.

Question 3(d). Any other information to strengthen the process of determining dose-response default positions.

More detail for the calculation of, for instance, the ED_{10} needs to be provided. Also, in cases where extrapolations are below the ED_{10}, such as with biologically based models, details are needed for the linear extrapolation below that level.

The breakout group offered specific recommendations on this subject.

Question 4(a). **The use of various parameters (e.g., toxicity incidence, biomarker levels) to give clues as to the shape of dose-response relationships in the observed range. What guidance can we provide on how to effectively use biomarkers that can be measured at low exposure levels?**

No answer; need illustrative examples.

Question 4(b). **What other guidance might be given as to the parameters that can be used and when and how to use them?**

For parameters to be used in biological models, a rationale must be provided stating that the parameters were collected in experimental conditions that are expected to be comparable to chronic bioassay conditions.

REFERENCES

Gaylor, D.W.; Kodell, R.L. (1980) Linear extrapolation algorithm for low-dose risk assessment of toxic substances. J. Environ. Pathol. Toxicol. 4:305-312.

Krewski, D.; Brown, C.; Murdoch, D. (1984) Determining "safe" levels of exposure: safety factors of mathematical models. Fund. Appl. Toxicol. 4:S383-S394.

Hazard Identification Breakout Group

Robin Fielder, Chair
Health Aspects of Environment and Food (Medical)
Department of Health
London, England

Samuel Cohen
Department of Pathology
and Microbiology
University of Nebraska
Medical Center
Omaha, NE

Nancy Kim
Division of Environmental
Health Assessment
New York State Department
of Health
Albany, NY

William Pease
Center for Occupational and
Environmental Health
University of California
Berkeley, CA

Rory Conolly
Inhalation Toxicology and
Biomathematical Modeling Chemical
Industry Institute of Toxicology
Research Triangle Park, NC

James Klaunig
Indiana University School of Medicine
Indianapolis, IN

M. Jane Teta
Health Safety and Environment
Union Carbide Corporation
Danbury, CT

Prior to considering the specific charge relating to hazard identification, the breakout group discussed general issues concerning risk assessment. At the initiation of discussion, the group recognized that the assigned topic area overlaps somewhat with topics assigned to other breakout groups. Based on the discussion, breakout group members found the following general principles to be important considerations with regard to the cancer risk assessment guidelines:

- The guidelines should establish a clear process for considering all available scientific information, identifying data gaps, and defining criteria that will govern how assessments will be reevaluated when new scientific information is available. EPA should establish a transparent process for encouraging the development and timely use of relevant information.

- For cases when only limited information is available, the guidelines should support an iterative process for making decisions based on whatever data are available.

- The guidelines should identify major default assumptions to be used in the absence of information, the rationale for these defaults, and the procedure for departing from defaults. EPA should consider the NRC recommendations regarding how default and alternative results should be described in the risk characterization and how specific defaults should be selected as the preferred option.

- Risk assessment is conducted according to a tiered process, with different degrees of information required for different types of regulatory decisions. The guidelines should address both data-poor and data-rich situations, with a clear description of the appropriate defaults in these cases.

The breakout group then considered a number of general issues concerning hazard identification before addressing the specific questions assigned to the group in the Charge to Workshop Reviewers (see Appendix B). The group raised the following points:

- EPA should expand the section of the guidelines on the value and use of epidemiological data, so that the risk assessment process recognizes that high-quality negative epidemiological data combined with sufficient mechanism of action information can overrule positive bioassay results.

- EPA should provide guidance on the criteria and process for evaluating the relevance of animal toxicity data to humans. The Agency's experience with alpha-2μ-macroglobulin and with the development of other supplemental documents offer possible models for this process.

- For cases where chronic toxicity data are limited, the breakout group participants endorsed EPA's proposal to classify potential carcinogens based on the results of validated short-term tests and other data (e.g., SAR data and narrative #4 in the proposed guidelines).

- EPA should adopt and describe a default procedure for prioritizing chemicals of concern on the basis of available non-chronic testing data (e.g., short-term bioassays, SAR).

- Any proposal for hazard identification based on limited non-chronic testing data should address the following issues: the relevance, sensitivity, and specificity of available genotoxicity tests, and how available pharmacokinetic data will be incorporated. The group also recommended development of a procedure to assign the most weight to *in vivo* mutagens. It also recommended the development of test methods for detecting other important modes of action but suggested that existing nongenotoxic tests provide an insufficient basis for identifying potential carcinogens.

- EPA should explain how expedited hazard identification decisions will be integrated in a tiered process with the more comprehensive hazard assessment process established by the proposed guidelines.

Members of the breakout group agreed that the draft guidelines provide a useful summary of hazard identification and welcomed the higher scientific content. Nonetheless, the need to improve some sections was noted. In particular, the group suggested that the coverage of epidemiology should include several descriptions of the advantages of well-conducted epidemiologic studies for hazard characterization (e.g., relevant species, exposure data in the dose range of interest, effects seen under conditions of human exposure). In the treatment of study quality, a clear distinction was sought between issues of validity (i.e., selection bias, information bias, and confounding) and issues of precision (i.e., power). According to the breakout group, imprecision does not render a study flawed, since a properly conducted meta-analysis can enhance the value of multiple valid-but-imprecise studies, irrespective of the outcome. A well-conducted data analysis, however is not a statistical exercise; rather, it involves a careful, qualitative assessment of available studies, a clear description of methodology employed, and appropriate attention to heterogenicity.

Although the guidelines no longer include a separate classification of the level of evidence from human and animal data, the assessment process, as currently described, does not encourage examination of consistencies, inconsistencies, and how information from human studies might refine or change conclusions from experimental data. Based on mode of action considerations, greater weight might be given to quality epidemiologic data in the presence of animal data of questionable relevance to humans. In addition, epidemiologic data also can be utilized to inform the dose-response process by addressing the plausibility of the experimental conclusions and/or indicating the most appropriate mode of action, shape of the dose-response curve, target organ, sex, or exposure for the dose-response assessment.

For testing plausibility, the animal-based estimate should be examined in the context of what has been obtained in epidemiologic studies using the extent-of-overlap of the respective confidence intervals as well as scientific judgment. The concept of providing an upper bound on risk based on the 95 percent upper confidence limit should be discouraged since it does not make use of meaningful data.

In addition to human epidemiologic data, the use of experimental data with human tissue is valuable in a number of areas (extrapolation and mechanistic data) and is a particularly important consideration in the "other data" section.

In response to the specific questions on hazard identification called out in the charge to reviewers, the breakout group provided the following comments:

Question 2a(1). Adequacy and utility of guidance on human studies.

- Need to expand section on epidemiologic data to provide a better balance versus animal data.
- Need to explain why epidemiologic data is important.
- Need to give broad treatment of only the types of data that are most useful.
- Need to modify the meta-analysis section. This is not simply a statistical exercise, but includes a descriptive analysis/assessment.
- Need to consider and distinguish validity (i.e., selection bias, information bias, and confounding) from precision (i.e., power).

Question 2a(2). Adequacy of animal data.

- Very reasonable. Guidelines are not intended to be a textbook or to consider interpretation of specific tumor sites.
- Need to expand maximum tolerated dose discussion. Also should recognize that MTD testing may produce results irrelevant to humans and increase sensitivity at the price of specificity.
- Concern was expressed in the group about the use of genetically modified strains in routine studies; group members suggested that the strains might be useful in generating mechanistic data, but not in testing bioassays.
- Need to consider on a case-by-case basis the significance of the induction of tumors at spontaneous tumor sites compared to rare sites.

Question 2a(3). Adequacy of other key evidence.

- Should endorse the need to consider the other data listed (e.g., short-term tests, SAR, pharmacokinetics data).
- Should give mutagenicity data more emphasis.

- Should use expert judgment in weight-of-evidence consideration of mutagenicity data.

- The demonstration of clear *in vivo* genotoxicity has real significance with respect to potential carcinogen.

Question 2(b). Pros and cons of using one-step rather than three-step hazard identification.

- Strong endorsement of one-step process with consideration of overall profile in one stage.

- Three-stage process is an artificial distinction and the last step is considered minor.

- It may be worth stating how new approaches will differ in practice from the present approach.

- Need to address human and experimental data inconsistencies.

Question 2(c). The proposal in making hazard decisions, to place more emphasis than before on evidence other than tumor data per se.

- Strong endorsement of the need to consider all the relevant data.

Question 2(d). Evaluate the merits and utility of using a narrative summary as a component of hazard identification.

- This was considered essential.

- It is appropriate for a narrative to be a primary product of hazard identification.

- This is the vehicle for explaining strengths and uncertainties.

Question 2(e). Recommendations for enhancing the presentation and utility of a narrative summary.

- It should be clear and precise.

- It should include consideration of strengths and uncertainties.

- The adoption of a common format would encourage consistency.

Question 2(f). **The arguments for and against using a classification system with standardized hazard descriptors versus a hazard summary without such a system and descriptors.**

Question 2(g). **The advantages and disadvantages of using three instead of six possible hazard classification descriptors.**

The breakout group considered these two questions together. The following conclusions were drawn:

- While many members of the group felt that a hazard narrative alone is preferable for providing a summary of available information on carcinogenic risk to humans, the group concluded that in the world of regulatory practice some abbreviated classification scheme would be required.

- Three categories are insufficient for classification purposes because they are too broad. The breakout group recommended that EPA consider a scheme with at least four classes that incorporate information about weight of evidence, conditions of exposure, and relevance to humans.

- The group saw merit in the NRC carcinogen categorization scheme developed in the recent report *Science and Judgment in Risk Assessment* (1994). Information for classification according to this scheme can be abstracted from EPA's proposed hazard narratives. The NRC categories are useful because they provide an indication of level of concern in regard to human risks and will facilitate the selection of extrapolation models. The group recommended that EPA consider a modification of the NRC system that more clearly incorporates weight of evidence into the NRC descriptors, which emphasize conditions of exposure and relevance. (see table 4-1).

- In addition, the advantages of international harmonization of classification schemes was recognized. Incompatible classification criteria between different countries leads to problems and should be avoided if possible.

REFERENCE

Committee on Risk Assessment of Hazardous Air Pollutants (1994) Science and judgment in risk assessment. Washington, DC: National Academy Press.

SECTION FIVE

HIGHLIGHTS OF PRELIMINARY AND OBSERVER COMMENTS

REVIEWERS' PRELIMINARY COMMENTS

Prior to the workshop, each expert reviewer was asked to review the draft cancer risk assessment guidelines and provide written comments. (Appendix B provides the Charge to Workshop Reviewers.) Relying on their technical knowledge and best professional judgment, reviewers responded with comments on:

- the benefits and limitations of using mode of action information to help identify hazards and develop dose-response relationships;
- the nature of the hazard identification process and classification system;
- dose-response evaluation in the observed dose range and at environmental exposure levels; and
- the use of default science policy positions in the risk assessment process.

The expert reviewers provided notably diverse comments, which was consistent with their distinct backgrounds and the specific objectives of the workshop. Various reviewers expressed the opinion that the draft guidelines should explain:

- the reasons for changing the guidelines;
- the consequences of changing the guidelines and the effect of the changes on current risk assessments;
- the way in which risk managers will use the revised guidelines; and
- the way in which the revised guidelines will address consistency in risk assessment practices across agencies.

Reviewers generally found that the draft guidelines were too qualitative and gave unequal treatment to hazard assessment versus dose-response and animal data versus human data. The most controversial topic among reviewers was default assumptions. Overall, the comments raised a number of issues for consideration at the workshop.

Comments on Mode of Action

Carol Henry, Ph.D., of the U.S. Department of Energy, reviewed the premeeting comments that focused on mode of action. Dr. Henry identified six major themes in reviewers' comments:

Mechanism issues:

- The overview of cancer process is incomplete:
  - more guidance is needed on proteins involved in cell cycle control and the role of cancer susceptibility genes in specific types of familial and sporadic cancers.
- The mode of action section does not reflect the full range and complexity of ways carcinogens may affect:
  - genes and gene products involved in cell cycle control; and
  - understanding of the regulation of apoptosis (i.e., programmed cell death).
- Nongenotoxic agents may have linear dose-response relationships:
  - agents acting via a cell-receptor mediated response or via interference with a DNA repair mechanism.
- Chemicals that induce somatic recombination (i.e., chromosome-chromosome interaction) are genotoxic but may not show up in standard test protocols.

Data requirements and data sufficiency:

- How much information will be needed to adequately justify using a nonlinear extrapolation technique?

- Are positive data (e.g., target organ toxicity) and negative data (e.g., absence of genotoxicity) equally important?
- Which are more important—pharmacokinetics or mechanism data (and how should the data be prioritized)?
- How can data from a chemical class be applied to a member of the class that has not been tested?

Uncertainty characterization:

- Treatment of uncertainty with regard to mode of action and causality is adequate.
- Guidance on statistical treatment of dose-response models is inadequate.
- No discussion is presented on additivity of effect or exposure within a mode of action or across modes of action.

Information use:

- Guidance on how the mode of action information would be related to numeric characterizations of risk is inadequate:
  - Will it be comparable to cancer potencies?
  - Will it look like a reference dose (RfD)?
- How will the additional information provided by mode of action judgments be incorporated into risk assessments and risk management decisions?
- Examples need to apply real chemicals to real world needs (e.g., a site cleanup).

Peer review issues:

- Decisions on mode of action will require considerable use of expert judgment.
- Use of expert judgment will require peer review for credibility.
- Peer review also will need to be a critical element in deciding about the robustness of mode of action information.

Logistics/process:

- How will these guidelines be used in regulatory programs (e.g., pesticides or European Community harmonization)?
- What will be the process for transitioning from the present risk assessment system to the new one?
- The proposed guideline revisions imply that modes of action can be established for regulated chemicals:
  - A larger data base will be required.
  - The time needed to conduct risk assessments is likely to increase.
- The distinction between scientific issues and policy judgments needs to be clarified.

Comments on Default Assumptions

The array of comments offered regarding default assumptions ranged from encouraging consistent use of default values to advocating that new information always be used. Marvin Schneiderman, Ph.D., of the National Academy of Sciences, summarized reviewers preliminary comments by posing the following questions:

- What new information is available that can be used in cancer risk assessment?
- Can regulatory decision-making be delayed while new information is generated?
- How much information is needed to formulate models?
- What additional toxicity information is needed to be predictive of effects?
- What information will reduce uncertainty?
- What information will lower the cost of establishing regulations?
- What effect will the emphasis on more expert judgment have on supporting EPA's regulatory actions?

Comments on Dose Response

Dose-response issues focused on two topics: fitting data into an observational range and extrapolation. Colin Park, Ph.D., of Dow Chemical Company, presented a summary of the premeeting comments on these topics. Reviewers expressed the opinion that the wording in the guidelines, referring to biologically based models as the default, implied considerable professional judgment. Reviewers asked:

- Is this realistic?
- Is the wording consistent with practice?
- What about secondary mechanisms?
- Is the wording merely a circular definition of default?
- What defaults are considered in dose response?
- What will the default be if biologically based models do not exist?

Dose-response extrapolations can use linear models, nonlinear models, or both. Guidance is needed, however, on how to differentiate between these models; if both models are used then an explanation of which model is more appropriate is needed. For example, when and how should the margin of exposure be used? The majority of reviewers supported the flexibility afforded in the revised guidelines but asked:

- What is the role of the LMS model?
- Should the ED_{10} or the benchmark dose $(BMD)_{10}$ be used?
- How should risk be presented (e.g., 10^{-4} or $ED_{10/10,000}$)?
- How does the linear model compare to the LMS or the Gaylor-Kodell model?

Comments on Hazard Identification

Robin Fielder, Ph.D., of the Department of Health, England, summarized reviewers comments on hazard identification. Although most reviewers' comments supported the proposed revision of the guidelines concerning treatment of human studies, animal studies, and other key evidence, one reviewer suggested that more case-specific guidance is needed on how to eliminate any ambiguous information. Concern also was expressed about the perceived diminished importance of quantitative data. Other reviewers were concerned that hazard assessment might encumber the regulatory process because the proposed guidelines call for consideration of all data. In regard to the guidance proposed for using the three sources of assessment data, guidance on the use of human data received the most criticism. Reviewer suggested the following:

- The main approaches used in conducting and considering the results from epidemiologic studies must be emphasized.
- The guidelines should specify the need for good quality exposure data.
- Giving power limitations of human studies even when other data (e.g., animal bioassay) are negative should be reconsidered.

Reviewers recognized that it is impractical (and undesirable) to consider interpretation of specific tumor types. They contend, however, that consideration of the following "generic" issues would improve the assessment:

- consideration of the significance of increases of tumors with appreciable spontaneous incidence;
- consideration of malignant and benign tumors together; and
- use of the maximum tolerated dose.

A number of reviewers suggested that the guidelines should recommend more caution with regard to modified strains of animals (i.e., increased susceptibility). Although all reviewers agreed that consideration of "other key evidence" (e.g., pharmacokinetics, structure-activity relationships) is important, one reviewer pointed out the need to distinguish between essential information and "nice to know" information. Additionally, the use of short-term test data in hazard identification was

encouraged. Although reviewers expressed the opinion that the importance of genotoxicity studies with regard to mechanisms should be emphasized, one reviewer felt that genotoxic assays are not sufficiently comprehensive. Reviewers favored considering nongenotoxic mechanisms on a case-by-case basis.

Reviewers supported EPA's proposal to use a one-step rather than a three-step approach to hazard identification. As proposed in the revised guidelines, other key evidence will now be considered in the overall profile of a substance along with all other relevant data. Reviewers also supported the guidelines' emphasis on data other than tumor data per se, pointing out that such data is critical for considering the mechanisms of carcinogenicity and the significance of experimental data to humans. Additionally, the use of all available data/scientific knowledge was universally supported.

Nearly all reviewers supported the merits and utility of including a succinct and clear narrative summary as a component of the hazard identification. Some suggested that a standard format would facilitate comparison of assessment results. Several reviewers expressed concern that some risk managers might focus exclusively on the narrative as the bottom line of the assessment. Also, one reviewer expressed concern that the proposed integrated approach to assessment will require more time and ultimately will be less effective for regulating carcinogens.

Reviewers commented that a standard "descriptor" is needed to accompany a classification system, arguing that this approach would be preferable to use of a hazard summary without such descriptors. Nonetheless, reviewers contended that hazard identification also needs to include a descriptive hazard summary. The need for standard descriptors depends in part on who will be using the information, a risk assessor or risk manager.

Although there was support among reviewers for reducing the number of hazard classification categories or descriptors, no consensus was reached on the number needed. Several reviewers supported the use of three categories (e.g., yes, no, do not know) because this approach would afford the advantage of simplicity, since risk managers often only look at the bottom line. Other reviewers had reservations about considering known, likely, and possible carcinogens in one group. This approach might result in more chemicals of some concern being placed in a sufficient data group. Reviewers emphasized the need for clear criteria along with guidance on how to use ancillary data

(i.e., not relating to tumor incidence) to change classification categories. Also, risk managers must have information on how to prioritize levels of concern.

OBSERVERS' COMMENTS

The workshop agenda included an opportunity for observers to make public statements during the plenary session held on Monday, September 12. Observers were asked to sign up if they intended to make a statement. At the discretion of each breakout group chair, observers also were provided an opportunity during breakout group sessions to participate in discussions.

Only one observer, John McCarthy, of the National Agricultural Chemicals Association, made a statement during the plenary session. Mr. McCarthy expressed the opinion that since industry conducts extensive testing of chemicals and has established a large data set, the guidelines should (hopefully) provide some flexibility in the use of all this data. He also advocated that the issue of high-dose testing should be addressed by EPA. Mr. McCarthy recommended that the guidelines more explicitly address the use of biologically based models (i.e., What kind and how much data are needed to use these models?). Also, Mr. McCarthy commented that the proposed use of a classification scheme with three categories might be insufficient. He recommended that EPA reconsider use of the four categories presented by NRC/NAS.

APPENDIX A

REVIEWER LIST

United States
Environmental Protection
Agency

Workshop on Cancer Risk Assessment Guidelines Issues

Hyatt Regency Reston
Reston, VA
September 12-14, 1994

Reviewer List

Henry Anderson
Chief Medical Officer
Bureau of Public Health
1414 East Washington Avenue
Room 96
Madison, WI 53703
608-266-1253
Fax: 608-267-4853

J. Carl Barrett
Director, Environmental
Carcinogenesis Program
National Institute for Environmental
Health Sciences
P.O. Box 12233 (MD C2-15)
Research Triangle Park, NC 27709
919-541-2992
Fax: 919-541-7784

Harvey Clewell
Senior Project Manager
ICF\Kaiser International
1201 Gaines Street
Ruston, LA 71270
318-255-4800
Fax: 318-255-4960

Samuel Cohen
Professor and Chairperson
Department of Pathology and
Microbiology
University of Nebraska Medical Center
600 South 42nd Street
Omaha, NE 68198-3135
402-559-6388
Fax: 402-559-9297

Murray Cohn
U.S. Consumer Product
Safety Commission
4330 East West Highway
Room 600C
Bethesda, MD 20814-4408
301-504-0994, ext. 1385
Fax: 301-504-0124

Rory Conolly
Inhalation Toxicology and
Biomathematical Modeling
Chemical Industry
Institute of Toxicology
6 Davis Drive
Research Triangle Park, NC 27709
919-558-1330
Fax: 919-558-1200

Robin Fielder
Chief Scientific Officer
Health Aspects of
Environment and Food (Medical)
Department of Health
Skipton House - Room 513A
80 London Road
Elephant and Castle
London SE1 6LW England
44-071-972-5322
Fax: 44-071-972-5156

Clay Frederick
Senior Research Fellow
Rohm & Haas Company
727 Norristown Road
Spring House, PA 19477-0904
215-641-7496
Fax: 215-619-1618 or 1621

Jay Goodman
Professor, Department of
Pharmacology and Toxicology
Michigan State University
B440 Life Sciences Building
East Lansing, MI 48824
517-353-9346
Fax: 517-353-8915

Carol Henry
Office of Integrated Risk Management
U.S. Department of Energy
1000 Independence Avenue, SW
Room 5A031
Washington, DC 20585
202-586-7150
Fax: 202-586-1492

Kim Hooper
Hazardous Materials Laboratory
California Environmental
Protection Agency
2151 Berkeley Way
Berkeley, CA 94704-1011
510-540-3499
Fax: 510-540-2305

Nancy Kim
Director
Division of Environmental
Health Assessment
New York State Department of Health
2 University Place - Room 350
Albany, NY 12203-3399
518-458-6435 or 6438
Fax: 518-458-6436

James Klaunig
Professor and Director of Toxicology
Indiana University School of Medicine
Medical Research Facility
1001 Walnut Street (MRF 003)
Indianapolis, IN 46202-5196
317-274-7824
Fax: 317-274-7787

John A. Moore
President and CEO
Institute for Evaluating Health Risks
1101 Vermont Avenue, NW
Suite 608
Washington, DC 20005-3521
202-289-8721
Fax: 202-289-8530

Colin Park
Health and Environmental Sciences
The Dow Chemical Company
1803 Building
Midland, MI 48674
517-636-1159
Fax: 517-636-1875

William Pease
Center for Occupational and
Environmental Health
School of Public Health
University of California - Berkeley
140 Warren Hall
Berkeley, CA 94720-7360
510-642-8853
Fax: 510-642-5815

Tore Sanner
Chief, Laboratory for Environmental
and Occupational Cancer
Institute for Cancer Research
The Norwegian Radium Hospital
Montebello
N-0310 Oslo 3, Norway
472-293-57-65
Fax: 472-293-57-67

Marvin A. Schneiderman
National Research Council
National Academy of Science
2101 Constitution Avenue, NW
(BEST MH 354)
Washington, DC 20418
202-334-3160

Peter Shields
Senior Clinical Investigator
Laboratory of Human Carcinogenesis
National Cancer Institute
37 Convent Drive
Building 37 - Room 2C16
Bethesda, MD 20892
301-496-1603 or 496-2048
Fax: 301-402-8577

Thomas B. Starr
Principal
ENVIRON International Corporation
7500 Rainwater Road
Raleigh, NC 27615-3700
919-876-0203
703-516-2300 (in Virginia)
Fax: 919-876-0201

Leslie Stayner
Assistant Director, Division of
Standards Development and
Technology Transfer (DSDTT)
National Institute for Occupational
Safety and Health
4676 Columbia Parkway (C-14)
Cincinnati, OH 45226-1998
513-533-8307
Fax: 513-533-8588

James Swenberg
Director, Curriculum in Toxicology
University of North Carolina
at Chapel Hill
South Columbia Street
Rosenau Hall - Room 357
Campus Box 7400
Chapel Hill, NC 27599
919-966-6139 or 6142
Fax: 919-966-6123

M. Jane Teta
Director of Epidemiology
Health Safety and Environment
Union Carbide Corporation
39 Old Ridgebury Road (K-3)
Danbury, CT 06817
203-794-5884
Fax: 203-794-5275

James Wilson
Director, Regulatory Affairs
Monsanto Company
800 North Lindbergh Boulevard
St. Louis, MO 63167
314-694-8879
Fax: 314-694-8808

Ronald Wyzga
Senior Program Manager
Health Studies Program
Electric Power Research Institute
3412 Hillview Avenue
Palo Alto, CA 94303
415-855-2577 or 2858
Fax: 415-855-1069

EPA Participants

William Farland
Director, Office of Health and
Environmental Assessment
U.S. Environmental Protection Agency
401 M Street, SW (8601)
Washington, DC 20460
202-260-7317
Fax: 202-260-0393

Richard Hill
Office of Prevention Pesticides and
Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW (7101)
Washington, DC 20460
202-260-2894
202-260-2897
Fax: 202-260-1847

Arnold Kuzmack
Office of Science and Technology
U.S. Environmental Protection Agency
401 M Street, SW (4301)
Washington, DC 20460
202-260-5821
Fax: 202-260-5394

Dorothy Patton
Risk Assessment Forum
U.S. Environmental Protection Agency
401 M Street, SW (8101)
Washington, DC 20460
202-260-6743
Fax: 202-260-3955

Harry Teitelbaum
Risk Assessment Forum
U.S. Environmental Protection Agency
401 M Street, SW (8101)
Washington, DC 20460
202-260-2782
Fax: 202-260-3955

Vanessa Vu
Deputy Director, Office of Pollution
Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, SW (7403)
Washington, DC 20460
202-260-1243
Fax: 202-260-1283

Jeanette Wiltse
Deputy Director, Office of Health and
Environmental Assessment
U.S. Environmental Protection Agency
401 M Street, SW (8601)
Washington, DC 20460
202-260-7315
Fax: 202-260-0393

William Wood
Risk Assessment Forum
U.S. Environmental Protection Agency
401 M Street, SW (8101)
Washington, DC 20460
202-260-6743
Fax: 202-260-3955

APPENDIX B

CHARGE TO WORKSHOP REVIEWERS

Charge to Workshop Reviewers

The current EPA cancer risk assessment guidelines were published in 1986. Changes in both our understanding of carcinogenesis and risk science since 1986 lead the Agency to seek changes in its cancer risk assessment process. The working draft revised guidelines attempts to encourage several changes in the EPA's approach to cancer risk assessment. Ofttimes the revisions emphasize, expand upon, or restate concepts that were included in the 1986 guidelines but were incompletely applied in practice. The draft asks assessors to take responsibility for conducting thorough analyses of reliable data on a case-by-case basis, to consider alternative positions, and to develop rationales for major judgments.

1.Mode of carcinogenic action (topic A; breakout group 1)

Although the use of mechanistic data in risk assessment has long been recognized as desirable, available data rarely demonstrate carcinogenic processes with any certainty. The 1986 cancer guidelines called for the evaluation of relevant information, but to date risk assessments seldom make full use of the available information, even when there may be enough to indicate a general mode of action.

The proposed guidelines call for analysis of mode of action information as a major basis for determining both human hazard and potential dose-response patterns. Along with the toxicology data physical, chemical and biological attributes of chemicals are evaluated for clues to the possible mode of action. For instance, among the various factors are the types and relative importance of genotoxic responses and influences on cell growth, death and differentiation. From these analyses, the assessor develops hypotheses about possible modes of carcinogenic action and the conditions of exposure where they operate. The strengths and weaknesses of the case for each possible mode of action are presented. The inferences about the possible mode(s) of action can then be used to judge whether cancer responses may occur in exposed humans and what might be the potential shape of the dose-response relationship at low doses.

Please comment on:

a. The proposed approach to use mode of action information for (1) hazard identification and (2) dose-response purposes:

b. To what extent will there be available information on chemical substances to make mode of action judgments?

c. What are the data elements in a mode of action review, and how can one assess the adequacy of case-specific information for developing mode of action positions?

d. The completeness of the guidance and illustrations in the draft for assessors to be able to make mode of action judgments. What additional guidance and illustrations may be useful?

e. Any other guidance on this topic for inclusion in the guidelines.

2. Hazard identification (topic E; breakout group 4)

Process: Current Agency guidelines call for a weight of evidence approach to human hazard identification, but in practice we often rely mainly upon tumor response data in humans and animals. Part of the problem may be the 3-step process that is currently used: categorize the evidence of carcinogenicity from studies in humans and studies in animals; classify as to human carcinogenicity; review all other potential inputs and reclassify, if needed. In current practice the third step receives little emphasis. The draft revisions use a 1-step hazard identification process which essentially coalesces all relevant inputs at one time into an overall weight-of-evidence determination. Reviews of component parts are completed and the quality of data evaluated as in the 1986 guidelines, but interim decisions on human hazard are not made.

Classification system: The present cancer guidelines employ an alphanumeric system of hazard classification adapted from a scheme originally developed by the International Agency for Research on Cancer. It uses 5 broad designations, with one of them divided into two parts: A--human carcinogen, B1/B2--probable human, C--possible human, D--not classifiable, E--non-carcinogenic. A narrative summary is to accompany each classification. Multiple problems have occurred in applying the existing classification system including but not limited to the difficulty in handling C carcinogens, in classifying agents where carcinogenic potential varies with the route of exposure, in classifying animal carcinogens that may not be carcinogenic in humans and in failing to use the narrative summary to reflect the confidence in the determinations.

The draft revision makes the classification of secondary importance to the narrative description of hazard potential. Hazard characterization includes a narrative summary which is uniquely tailored to each case, giving a synopsis of the hazard case with it strengths, weaknesses, uncertainties and applied default science policy positions; the anticipated mode of action with any limitations of its expression (exposure route/pattern); the hazard classification descriptor; and guidance for dose-response assessment. The draft also proposes a classification system using only three hazard descriptors: known or likely to be a human carcinogen, unlikely to be a human carcinogen, and cannot determine the carcinogenic potential for humans.

Please comment on:

a. The adequacy and utility of the guidance given concerning the review of (1) human studies, (2) animal studies and (3) other key evidence.

b. The pros and cons of using a 1-step instead of a 3-step hazard identification process?

c. The proposal, in making hazard decisions, to place more emphasis than before on evidence other than tumor data per se.

d. Evaluate the merits and utility of using a narrative summary as a component of hazard identification.

e. Recommendations for enhancing the presentation and utility of the narrative summary.

f. The arguments for and against using a classification system with standardized hazard descriptors versus a hazard summary without such a system and descriptors.

g. The advantages and disadvantages of using 3 instead of 6 possible hazard classification descriptors?

3. Low level dose-response extrapolation (topic D; breakout group 3)

The 1986 cancer guidelines and the present draft call for use of the best biologically based dose-response models. In the absence of a mechanistic model, the previous guidelines use the linearized multistage procedure as a default to project potential risks at low doses. In practice the Agency has almost always resorted to using this default procedure in exclusion of alternative positions. To better incorporate whatever mode of action considerations are available as well as to honestly indicate that low-dose projections are most often really judgment calls, the draft presents three potential default dose-response procedures--linear, non-linear and both. The option chosen depends upon the information at hand.

Please comment on:

a. How and whether biologically based models can be applied generically in risk assessments or can decisions only be approached on a case-by-case basis? What guidance might be given as to when and how to apply them?

b. Whether it is rational today to use the 3 stated default methods for dose-response extrapolation or other methods.

c. The adequacy of the information and illustrations given to assessors in the draft so that they can ably select default dose-extrapolation procedures.

d. Any other information to strengthen the process of determining dose-response default positions?

4. Observed range dose-response relationships (topic C; breakout group 3)

Currently the Agency relies on cancer incidence data to determine the shape of the dose-response curve in the observed range and to extrapolate down to lower human exposure levels. the linearized multistage procedure is the mainstay for evaluating data from experimental animals. The review draft recognizes the difficulty in estimating risks for cases where there is no biologically based model. It calls for the use and modeling of various types

of information (not cancer incidence alone) in the observed range and determining a point of departure for employing default extrapolation procedures (item 2 above) at lower exposure levels.

Please comment on:

a. The use of various parameters (e.g., toxicity incidence, biomarker levels) to give clues as to the shape of dose-response relationships in the observed range. What guidance can we provide on how to effectively use biomarkers that can be measured at low exposure levels?

b. What other guidance might be given as to the parameters that can be used and when and how to use them?

5. Use of science policy default positions (topic B; breakout group 2)

The 1986 cancer guidelines employed a number of default science policy positions to be used in the absence of generic or case-specific information. This includes many types of explicit or implicit defaults such as the use of animals as surrogates for humans, the pooling of malignant and benign tumors, and the use of an interspecies potency scaling factor. In the main, these default positions were conservative, that is, risk averse in nature. Little information was given as to when and how to deviate from the defaults, with the result being that in practice assessments almost always included a number of default positions to the exclusion of using case-specific information.

A 1994 National Research Council report to the Agency on risk assessment practices recognized that defaults are necessary in the assessment process but recommended that criteria be developed as to when to deviate from them. The present draft guidelines take the position that in the face of data gaps and uncertainties on important issues, assessors should (1) make maximum use of reliable data on chemicals, (2) evaluate options for handling them and (3) articulate rationales for the judgmental approaches taken, whether they are any particular defaults or alternative positions. The adequacy of reasoning would be evaluated during the peer review of the assessment.

Please comment on:

a. The Agency's general approach to the use of defaults in risk assessment and especially on the emphasis to evaluate science policy options on a case-by case basis.

b. The extent to which the guidelines identify the major sources of uncertainty in risk assessments and the appropriateness and scientific adequacy of the defaults proposed.

APPENDIX C

WORKSHOP AGENDA

United States
Environmental Protection
Agency

Workshop on Cancer Risk Assessment Guidelines Issues

Hyatt Regency Reston
Reston, VA
September 12-14, 1994

Workshop Agenda

MONDAY SEPTEMBER 12

7:30AM Registration and Onsite Check-In

Plenary Session

8:30AM **Introduction to the Guidelines Revisions**
Jeanette Wiltse, U.S. Environmental Protection Agency, Office of Health and Environmental Assessment

9:00AM **Highlights of Premeeting Comments and Charge to the Breakout Groups**
Workshop Chair: Ron Wyzga
Breakout Group Chairs: Carol Henry, Marvin Schneiderman, Colin Park, and Robin Fielder

10:15AM Break

Breakout Group Sessions

10:30AM **Breakout Groups Convene to Discuss Lead Topics**

	Group #1	Group #2	Group #3	Group #4
Lead Topic:	**Topic A: Mode of Action**	**Topic B: Default Assumptions**	**Topic C&D: Dose Response**	**Topic E: Hazard Identification**
Chairs:	Carol Henry	Marvin Schneiderman	Colin Park	Robin Fielder
Members:	Henry Anderson Carl Barrett Clay Frederick Tore Sanner Jim Swenberg Ron Wyzga	Kim Hooper Jack Moore Peter Shields Leslie Stayner James Wilson	Murray Cohn Harvey Clewell Jay Goodman Tom Starr	Sam Cohen Rory Conolly Nancy Kim Jim Klaunig Bill Pease Jane Teta
EPA:	Richard Hill	Jeannette Wiltse	Arnold Kuzmack	Vanessa Vu

MONDAY SEPTEMBER 12 (continued)

12:00PM Lunch

1:30PM **Breakout Groups Reconvene**

3:30PM **Observer Comments to Breakout Groups**

3:45PM Break

Plenary Session

4:00PM **Preliminary Breakout Group Reports on Lead Topics**
Breakout Group Chairs

5:00PM **Observer Comments to Plenary**

5:30PM Adjourn

TUESDAY SEPTEMBER 13

Breakout Group Sessions

8:30AM **Breakout Groups Convene to Discuss and Respond to Day One Lead Topic Presentations (note new topic assignments)**

	Group #1	Group #2	Group #3	Group #4
Second Topic:	**Topic E: Hazard Identification**	**Topic A: Mode of Action**	**Topic B: Default Assumptions**	**Topic C&D: Dose Response**
Chairs:	Carol Henry	Marvin Schneiderman	Colin Park	Robin Fielder

10:30AM Break

Plenary Session

11:00AM **Breakout Group Reports Responding to Day One Lead Topics**
Breakout Group Chairs

12:00PM **Discussion by Reviewers**

12:30PM Lunch

TUESDAY SEPTEMBER 13 (continued)

Breakout Group Sessions

2:00PM **Breakout Groups Reconvene to Summarize and Integrate Comments and Recommendations to the Agency on Lead Topics**

	Group #1	Group #2	Group #3	Group #4
Lead Topic:	**Topic A: Mode of Action**	**Topic B: Default Assumptions**	**Topic C&D: Dose Response**	**Topic E: Hazard Identification**
Chairs:	Carol Henry	Marvin Schneiderman	Colin Park	Robin Fielder

5:00PM Adjourn

WEDNESDAY SEPTEMBER 14

Plenary Session

9:00AM **Final Breakout Group Summary Reports and Recommendations**
Breakout Group Chairs
- Group #1 - Topic A: Mode of Action, Carol Henry
- Group #2 - Topic B: Default Assumptions, Marvin Scheiderman

10:15AM Break

10:45AM **Final Breakout Group Summary Reports and Recommendations (continued)**
Breakout Group Chairs
- Group #3 -Topics C & D: Dose Response, Colin Park
- Group #4 - Topic E: Hazard Identification, Robin Fielder

11:45AM **Workshop Chair's Summary**
Ron Wyzga, Workshop Chair

12:00PM Adjourn

APPENDIX D

REVIEWER BREAKOUT GROUP ASSIGNMENTS

United States
Environmental Protection
Agency

Workshop on Cancer Risk Assessment Guidelines Issues

Reviewer Breakout Group Assignments

Topics for breakout groups:

A = mode of action
B = default assumptions
C = dose response assessment in the observed range
&
D = dose response extrapolation outside the observed range
E = hazard identification

	Group #1	Group #2	Group #3	Group #4
Lead Topic:	Topic A: Mode of Action	Topic B: Default Assumptions	Topic C&D: Dose Response	Topic E: Hazard Identification
Second Topic:	Topic E: Hazard Identification	Topic A: Mode of Action	Topic B: Default Assumptions	Topic C&D: Dose Response
Chairs:	Carol Henry	Marvin Schneiderman	Colin Park	Robin Fielder
Members:	Henry Anderson Carl Barrett Clay Frederick Tore Sanner Jim Swenberg Ron Wyzga	Kim Hooper Jack Moore Peter Shields Leslie Stayner James Wilson	Murray Cohn Harvey Clewell Jay Goodman Tom Starr	Sam Cohen Rory Conolly Nancy Kim Jim Klaunig Bill Pease Jane Teta
EPA:	Richard Hill	Jeannette Wiltse	Arnold Kuzmack	Vanessa Vu

NOTE:

Lead Topic: Prior to the workshop, each breakout group's primary responsibility was to review the guidelines, preparing premeeting comments with particular emphasis on their lead topic issues. On site, during the breakout sessions, the breakout groups will discuss the lead topic in relation to the guidelines and prepare oral and written summary reports.

Second Topic: On site, on Tuesday, September 13, the breakout groups will reconvene and shift focus to review another breakout group's Day One summary (as assigned above). Each breakout group chair will present a synopsis of this discussion in a plenary session.

APPENDIX E

FINAL OBSERVER LIST

United States
Environmental Protection
Agency

Workshop on Cancer Risk Assessment Guidelines Issues

Hyatt Regency Reston
Reston, VA
September 12-14, 1994

Final Observer List

Ruth Allen
Environmental Epidemiologist
U.S. Environmental Protection Agency
401 M Street, SW (7509C)
Washington, DC 20460
703-308-2918
Fax: 703-305-5147

John Allshouse
Staff Engineer
Everest Consulting Associates
15 North Main Street
Cranbury, NJ 08512
609-655-7426
Fax: 609-655-5637

Darryl Arfsren
Staff Scientist
Karch & Associates, Inc.
1701 K Street, NW - Suite 1000
Washington, DC 20006
202-463-0400
Fax: 202-463-0502

Charles Axten
Staff Vice President
Health, Safety &
Environmental Affairs
North American Insulation
Manufacturers Association
44 Canal Central Plaza - Suite 310
Alexandria, VA 22314
703-684-0084
Fax: 703-684-0427

Lesa Aylward
Senior Staff Scientist
Karch & Associates
1701 K Street, NW - Suite 1000
Washington, DC 20006
202-463-0400
Fax: 202-463-0502

Donald Barnes
Staff Director, Science Advisory Board
Office of the Administrator
U.S. Environmental Protection Agency
401 M Street, SW (A-101)
Washington, DC 20460
202-382-4126
Fax: 202-382-7884

Leila Barraj
Statistician
TAS, Inc.
1000 Potomac Street, NW
Washington, DC 20007
202-337-2625
Fax: 202-337-1744

Lisa Barrera
Senior Vice President
Barrera Associates, Inc.
733 15th Street, NW - Suite 1120
Washington, DC 20005
202-638-6631
Fax: 202-638-4063

James Barter
Halogenated Solvents
Industry Alliance
2001 L Street - Suite 506A
Washington, DC 20036
202-775-0232
Fax: 202-833-0381

Jim Barter
Manager, Industrial Hygiene &
Health Toxicology
PPG Industry
One PPG Place
Pittsburgh, PA 15272
412-434-2801
Fax: 412-434-2137

David Bayliss
Epidemiologist
Human Health Assessment Group
Office of Research & Development
U.S. Environmental Protection Agency
401 M Street, SW (8602)
Washington, DC 20460
202-260-6765
Fax: 202-260-3803

Richard Belzer
Economist
U.S. Office of Management & Budget
New Executive Office Building
Room 10202
Washington, DC 20503
202-395-3084
Fax: 202-395-7285

Gershon Bergeisen
Health Science Advisor
Superfund Branch
U.S. Environmental Protection Agency
401 M Street, SW (5204G)
Washington, DC 20460
703-603-8816
Fax: 703-603-9104

Martin Bernstein
Manager, Toxicology
CIBA
Ardsley, NY 10502
914-479-2765
Fax: 914-478-4839

Matthew Bogdanffy
Manager, Biochemical Toxicology &
Risk Analysis
Dupont
P.O. Box 50
Newark, DE 19714
302-366-5011
Fax: 302-366-5003

John Bowers
Mathematical Statistician
U.S. Food & Drug Administration
200 C Street, SW
Washington, DC 20204
202-205-5065
Fax: 202-260-0891

Daniel Boyd
President
Daniel T. Boyd & Company
505 Wye Hall Drive
Queenstown, MD 21658
410-827-6244
Fax: 410-827-7589

Eletha Brady-Roberts
Environmental Scientist
U.S. Environmental Protection Agency
26 West Martin Luther King Drive
Cincinnati, OH 45268
513-569-7662
Fax: 513-569-7916

Nancy Bryson
Corwell & Moring
1001 Pennsylvania Avenue, NW
Washington, DC 20004
202-624-2529
Fax: 202-628-5116

Gary Burin
Toxicologist
Technology Sciences Group
1101 17th Street, NW - Suite 500
Washington, DC 20036
202-828-8980
Fax: 202-872-0745

William Burnam
Branch Chief, Science Analysis Branch
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
703-305-7491
Fax: 703-305-5147

William Butler
British Institute for
Biological Research
P.O. Box 8598
Philadelphia, PA 19101
215-739-4499
Fax: 215-423-9210

Daniel Byrd
President
CTRAPS
400 Virginia Avenue, SW
Suite C-110
Washington, DC 20024
202-554-0807
Fax: 202-484-6019

Paul Cammer
President
Cammer & Associates
2000 L Street, NW - Suite 730
Washington, DC 20036
202-223-5904
Fax: 202-223-5979

Lee Casey
Attorney
Hunton & Williams
2000 Pennsylvania Avenue, NW
9th Floor
Washington, DC 20006
202-955-1564
Fax: 202-778-2201

Gail Charnley
National Research Council
2101 Constitution Avenue, NW
Washington, DC 20418
202-334-2689
Fax: 202-334-2752

Ruth Chen
Encotech
3985 Research Park Drive
Ann Arbor, MI 48108
313-761-1389
Fax: 313-761-1034

William Chen
Global Risk Assessment Manager
DowElanco
9330 Zionsville Road
Indianapolis, IN 46268-1054
317-337-3462
Fax: 317-337-4966

Mark Churchill
Legal Assistant
Crowell & Moring
1001 Pennsylvania Avenue, NW
Washington, DC 20004-2595
202-624-2953

David Clarke
Chief Editor
Risk Policy Report
Inside EPA
1225 Jefferson Davis Highway
Suite 1400
Arlington, VA 22202
703-416-8564
Fax: 703-416-8543

Eric Clegg
Reproductive Toxicologist
Office of Research & Development
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
202-260-8914
Fax: 202-260-8719

Charles Cochran
Attorney
Arnold & Porter
1200 New Hampshire Avenue, NW
Washington, DC 20036
202-872-5716
Fax: 202-872-6720

Jim Cogliano
Statistician/Branch Chief
Human Health Assessment Group
U.S. Environmental Protection Agency
401 M Street, SW (8602)
Washington, DC 20460
202-260-2575
Fax: 202-260-3803

Marian Copley
Section Chief, Toxicology Branch
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW (7509C)
Washington, DC 20460
703-305-7712
Fax: 703-305-5147

Steven Cragg
ToxTemps
22626 Glenn Drive - Suite 303
Sterling, VA 20164
703-709-8191
Fax: 703-709-8192

Thomas Crisp
Biologist
Office of Research & Development
U.S. Environmental Protection Agency
401 M Street, SW (8602)
Washington, DC 20460
202-260-3860
Fax: 202-260-8719

Kowetha Davidson
Scientist
Oak Ridge National Laboratory
1060 Commerce Park (MS-6480)
Oak Ridge, TN 37830
615-574-7799
Fax: 615-574-9888

Kerry Dearfield
Supervisory Pharmacologist
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW (7509C)
Washington, DC 20460
703-305-6780
Fax: 703-305-5453

Elizabeth Doyle
Toxicologist
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW (7509C)
Washington, DC 20460
703-305-2722
Fax: 703-305-5453

Julie Du
Toxicologist
Office of Water
U.S. Environmental Protection Agency
401 M Street, SW (4304)
Washington, DC 20460
202-260-7583
Fax: 202-260-1036

Paul Dugard
Regulatory Affairs Manager
ICI Americas, Inc.
3411 Silverside Road - P.O. Box 15391
Wilmington, DE 19850
302-887-4344
Fax: 302-887-7706

Clifford Elcombe
Zeneca
Alderley Park Macclesfield
Cheshire SK 10 4TJ
England
62-55-15456
Fax: 62-55-82897

Reto Engler
Senior Science Advisor
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW (H7509C)
Washington, DC 20460
703-308-7328
Fax: 703-305-5147

Toni Fedorowski
Senior Manager, Regulatory Services
Church & Dwight Company, Inc.
469 North Harrison Street
Princeton, NJ 08540
609-683-5900
Fax: 609-497-7168

Penny Fenner-Crisp
Deputy Director
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW (7501C)
Washington, DC 20460
703-305-7092
Fax: 703-305-6244

John Festa
Senior Scientist
American Forest & Paper Association
1111 19th Street, NW - Suite 800
Washington, DC 20036
202-463-2587
Fax: 202-463-2423

Karl Gabriel
Consultant
British Institute for
Biological Research
P.O. Box 8598
Philadelphia, PA 19101
215-739-4499
Fax: 215-423-9210

Glenn Gamber
Pesticides and Toxic Chemical News
1101 Pennsylvania Avenue,SE
Washington, DC 20003
202-544-1980

Laura Giese
Project Scientist
Environmental Resources
Management, Inc.
855 Springdale Drive
Exton, PA 19341
610-524-3784
Fax: 610-524-7798

Carol Gillis
Associate Toxicologist
ChemRisk
Stroudwater Crossing
1685 Congress Street
Portland, ME 04102
207-774-0012
Fax: 207-774-8263

George Gray
Scientist
Harvard Center for Risk Analysis
718 Huntington Avenue
Boston, MA 02115
617-432-4341
Fax: 617-432-0190

Stanley Greenfield
Senior Vice President
Systems Applications International
101 Lucas Calley Road
San Rafael, CA 94903
415-507-7100
Fax: 415-507-7177

David Hanson
Head, Washington News Bureau
Chemical & Engineering News
1155 16th Street, NW
Washington, DC 20036
202-872-4495
Fax: 202-872-8727

John Hanson
Attorney
Beveridge & Diamond
1350 I Street, NW
Washington, DC 20005
202-789-6000
Fax: 202-789-6190

Frank Hawk
Manager, Toxicological Services
Borden, Inc.
1105 Schrock Road - Suite 401
Columbus, OH 43229
614-431-6615
Fax: 614-431-6611

Sara Henry
Toxicologist
U.S. Food & Drug Administration
200 C Street, SW (HFS308)
Washington, DC 20204
202-205-8705
Fax: 202-205-4422

Karen Hentz
Senior Staff Scientist
Karch & Associates
1701 K Street, NW - Suite 1000
Washington, DC 20006
202-463-0400
Fax: 202-463-0502

Luis Hernandez
Senior Research Associate
Barrera Associates
733 15th Street, NW - Suite 1120
Washington, DC 20005
202-638-6631
Fax: 202-638-4063

Oscar Hernandez
Chief, Chemical Screening &
Risk Assessment Division
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
202-260-3442
Fax: 202-260-1216

Thomas Hesterberg
Senior Toxicologist
Schuller International, Inc.
P.O. Box 625005
Littleton, CO 80162-5005
303-978-3831
Fax: 303-978-2358

Charlie Hiremath
Human Health Assessment Group
Office of Health Effects Assessment
U.S. Environmental Protection Agency
401 M Street, SW (8602)
Washington, DC 20460
202-260-5725
Fax: 202-260-3803

Karen Hogan
Statistician
Health Effects Division
Office of Pollution Prevention & Toxics
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
202-260-3895
Fax: 202-260-1279

Vicki Hutson
Project Director
Abt Associates Inc.
4800 Montgomery Lane
Hampden Square - Suite 500
Bethesda, MD 20814-5341
301-913-0500
Fax: 301-652-7530

Stephanie Irene
Deputy Director
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW (H7509C)
Washington, DC 20460
703-305-5004
Fax: 703-305-5147

Cindy Jengeleski
Manager, Scientific Programs
American Industrial Health Council
2001 Pennsylvania Avenue, NW
Suite 760
Washington, DC 20006
202-833-2183
Fax: 202-833-2201

Jennifer Jinot
Toxicologist
Human Health Assessment Group
U.S. Environmental Protection Agency
401 M Street, SW (8602)
Washington, DC 20460
202-260-2575
Fax: 202-260-3803

Larry Kaiser
Graduate Assistant
Georgetown University
1020 North Quincy Street
Apartment 706
Arlington, VA 22201
703-524-2765

Alan Katz
Executive Director
Technical Assessment Systems, Inc.
1000 Potomac Street, NW
Washington, DC 20007
202-337-2625
Fax: 202-337-1744

Susan Keane
Abt Associates, Inc.
4800 Montgomery Lane
Hampden Square - Suite 500
Bethesda, MD 20814
301-913-0505
Fax: 301-652-7530

Anson Keller
EA Engineering & Science Technology
8401 Colesville Road - Suite 500
Silver Spring, MD 20910
301-565-4216
Fax: 301-587-4752

John Keller
Senior Scientist
Apex Environmental, Inc.
15850 Crabbs Ranch Way - Suite 300
Rockville, MD 20855
301-417-0200
Fax: 301-975-0169

Jim Knaak
Halogenated Solvents
Industry Alliance
2001 L Street - Suite 506A
Washington, DC 20036
202-775-0232
Fax: 202-833-0381

John Kneiss
Senior Manager
Synthetic Organic Chemical
Manufacturers Association
1330 Connecticut Avenue, NW
Suite 300
Washington, DC 20036
202-822-6766
Fax: 202-659-1699

Aparna Koppikar
Epidemiologist
Human Health Assessment Group
Office of Research & Development
U.S. Environmental Protection Agency
401 M Street, SW (8602)
Washington, DC 20460
202-260-6765
Fax: 202-260-3803

James Lamb
Vice President
Jellinek, Schwartz & Connolly, Inc.
1525 Wilson Boulevard - Suite 600
Arlington, VA 22209
703-527-1670
Fax: 703-527-5477

Sandra Lang
Director, National Toxicology
Program Liaison Office
National Institute for
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709
919-541-0530
Fax: 919-541-0295

Frank Letkiewicz
Senior Project Manager
Abt Associates, Inc.
4800 Montgomery Lane
Hampden Square - Suite 500
Bethesda, MD 20814
301-913-0521
Fax: 301-652-7530

Steven Lewis
Toxicologist
Exxon Biomedical Sciences
Mettlers Road (CN2350)
East Millstone, NJ 08875-2350
908-873-6063
Fax: 908-873-6009

Yi-Jong Lin
Senior Research Associate
Colgate Palmolive Company
909 River Road
Piscataway, NJ 08855
908-878-7793
Fax: 908-878-7844

Bertram Litt
Litt Associates
3612 Veazey Street, NW
Washington, DC 20008
202-686-0191
Fax: 202-686-0194

Janice Longstretch
Risk Program Director
Water Policy Institute
555 Quince Orchard Road - Suite 600
Gaithersburg, MD 20878-1437
301-990-3034
Fax: 301-990-1650

Po-Yung Lu
Head, Biomedical & Environmental
Information Analysis
Oak Ridge National Laboratory
1060 Commerce Park (MS-6480)
Oak Ridge, TN 37830
615-574-7803
Fax: 615-574-9888

I. Lusis
Senior Staff Scientist
Lockheed Environmental Systems &
Technology Company
1901 North Fort Myer Drive - Suite 305
Arlington, VA 22209
703-516-9091
Fax: 703-516-9050

Elizabeth Margosches
Chief, Quantitative Methods
Health Effects Division
Office of Pollution Prevention & Toxics
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
202-260-1511
Fax: 202-260-1279

Keith Matthews
Attorney
Weinberg, Bergeson & Neuman
1300 I Street, NW - Suite 1000W
Washington, DC 20005
202-962-8585
Fax: 202-962-8599

Mark Mayes
ARCO Chemical Company
16 Campus Square Boulevard
Room 327
Newtown Square, PA 19073
610-359-4855
Fax: 610-359-4865

John McCarthy
Vice President
National Agricultural
Chemicals Association
1156 15th Street, NW - Suite 400
Washington, DC 20005
202-872-3876
Fax: 202-463-0474

Robert McGaughy
Senior Scientist
Office of Research & Development
U.S. Environmental Protection Agency
401 M Street, SW (8602)
Washington, DC 20460
202-260-5889
Fax: 202-260-3803

Jane Moody Rachal
Chief Editor
Inside EPA
1225 Jefferson Davis Highway
Suite 1400
Arlington, CT 22202
703-416-8536
Fax: 703-416-8543

Ronald Mull
Senior Regulatory Toxicologist
Dupont
Barley Mill Plaza - P.O. Box 80038
Willmington, DE 19880-0038
302-992-6272
Fax: 302-992-6470

Daniel Mulveny
Research Assistant
Karch & Associates
1701 K Street, NW - Suite 1000
Washington, DC 20006
202-463-0400
Fax: 202-463-0502

W.C. Norman
Partner
Patton Boggs
2550 M Street, NW
Washington, DC 20037
202-457-5270
Fax: 202-457-6315

Edward Ohanian
Chief, Human Risk Assessment Branch
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
202-260-7571
Fax: 202-260-1036

Steve Olin
Deputy Director
Risk Science Institute
International Life Sciences Institute
1126 16th Street, NW
Washington, DC 20036
202-659-3306
Fax: 202-659-3617

Mary Paxton
American Petroleum Institute
1220 L Street, NW
Washington, DC 20005
202-682-8338
Fax: 202-682-8270

Dan Pedersen
Regulatory Engineer
American Water Works Association
1401 New York Avenue - Suite 640
Washington, DC 20005-2102
202-628-8303
Fax: 202-628-2846

Hugh Pettigrew
Section Head, Statistics Section
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
703-305-7491
Fax: 703-305-5147

Whang Phang
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW (H7509C)
Washington, DC 20460
703-305-6121
Fax: 703-305-5147

Sheldon Pine
General Counsel
North American Insulation
Manufacturers Association
44 Canal Central Plaza - Suite 310
Alexandria, VA 22314
703-684-0084
Fax: 703-684-0427

Tim Powers
Statistician
Roth Associates
6115 Executive Boulevard
Rockville, MD 20852
301-770-4405
Fax: 301-770-9248

Terry Quill
Attorney
Beveridge & Diamond
1350 I Street, NW
Washington, DC 20005
202-789-6061
Fax: 202-789-6190

Gerhard Raabe
Director, Epidemiology &
Medical Information Services
Mobil Oil Corporation
P.O. Box 1038
Princeton, NJ 08543-1038
609-737-6122
Fax: 619-737-6140

Alan Raul
Attorney
Beveridge & Diamond
1350 I Street, NW
Washington, DC 20005
202-789-6000
Fax: 202-789-6190

German Reyes
Senior Analyst
Office of Technology Assessment
U.S. Congress
Washington, DC 20510-8025
202-228-6851
Fax: 202-228-6833

Esther Rinde
Manager, Cancer Peer Review
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
703-305-7491
Fax: 703-305-5147

Charlie Ris
Deputy Director
Human Health Assessment Group
Office of Research & Development
U.S. Environmental Protection Agency
401 M Street, SW (8602)
Washington, DC 20460
202-260-6765
Fax: 202-260-3803

Margaret Rita
2208 Chestertown Drive
Vienna, VA 22182
703-641-5952

Alan Roberson
Director, Regulatory Affairs
American Waterworks Association
1401 New York Avenue, NW
Suite 640
Washington, DC 20005
202-628-8303
Fax: 202-628-2846

Denise Robinson
Scientific Director
International Life Sciences Institute
1126 16th Street, NW
Washington, DC 20036
202-659-3306
Fax: 202-659-3617

Ken Rock
Senior Environmental Engineer
Scienctech, Inc.
600 Maryland Avenue, SW - Suite 240
Washington, DC 20024
202-488-1464
Fax: 202-488-1964

Frank Rogers
Research Meteorologist
Mobil Research &
Development Corporation
600 Billingsport Road
Paulsboro, NJ 08066
609-224-3310
Fax: 609-224-3614

Samuel Rondberg
Science Advisory Board
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 02460

Fred Rothwarf
President
Applied Technology Enterprises, LTD
11722 Indian Ridge Road
Reston, VA 22091
703-758-0247
Fax: 703-620-1784

Margaret Round
Program Analyst
Northeast States for Coordinated
Air Use Management
129 Portland Street - Suite 501
Boston, MA 02114
617-367-8540
Fax: 617-742-9162

Dana Sargent
Toxicologist
Registration & Regulatory Affairs
Zeneca Products
1800 Concord Pike
Wilmington, DE 19897
302-886-5549
Fax: 302-886-1572

Rama Sastry
Statistician
U.S. Department of Energy
1000 Independence Avenue, SW
(EH-33)
Washington, DC 20585
301-903-4664
Fax: 301-903-8817

Rita Schoeny
Associate Director
Environmental Criteria &
Assessment Office
U.S. Environmental Protection Agency
26 West Martin Luther King Drive
Cincinnati, OH 45268
513-569-7544
Fax: 513-569-7475

Cheryl Scott
Epidemiologist
Human Health Assessment Group
Office of Research & Development
U.S. Environmental Protection Agency
401 M Street, SW (8602)
Washington, DC 20460
202-260-6765
Fax: 202-260-3803

Molly Shaffer
Attorney
Swidler & Berlin
3000 K Street, NW - Suite 300
Washington, DC 20007
202-424-7592
Fax: 202-424-7643

Betsy Shirley
Executive Director, Styrene
Information & Research Center
Society of Plastics Industry
1275 K Street, NW - Suite 400
Washington, DC 20005
202-371-5299
Fax: 202-371-1784

Charles Simmons
Attorney
Kilpatrick & Cody
700 13th Street, NW - Suite 800
Washington, DC 20005
202-508-5806
Fax: 202-508-5858

Dharm Singh
Toxicologist
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
202-260-5958
Fax: 202-260-3803

Danny Smith
Manager
Environmental Risk Management
Scienctech, Inc.
600 Maryland Avenue, SW - Suite 240
Washington, DC 20024
202-488-1464
Fax: 202-488-1964

Jacqueline Smith
Section Head
Exxon Biomedical Sciences, Inc.
Mettlers Road (CN-2350)
East Millstone, NJ 08875
908-873-6261
Fax: 908-873-6009

Susan Snider
Assistant Manager
Environmental Affairs
American Forest & Paper Association
1111 19th Street, NW - Suite 800
Washington, DC 20036
202-463-2589
Fax: 202-463-2423

Jack Snyder
Manager, Scientific Affairs
Society of Plastics Industry
1275 K Street, NW - Suite 400
Washington, DC 20005
202-371-5299
Fax: 202-371-1784

Clare Stine
Risk Assessment Forum
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Robert Tardiff
Vice President
EA Engineering & Science Technology
8401 Colesville Road - Suite 500
Silver Spring, MD 20910
301-565-4216
Fax: 301-587-4752

Edlu Thom
Director, Federal Government Relations
ARCO Chemical Company
601 Pennsylvania Avenue, NW
Suite 400
Washington, DC 20004
202-879-9288
Fax: 202-879-9287

David Thomas
Staff Associate, Environmental Policy
American Chemical Society
1155 16th Street, NW
Washington, DC 20036
202-872-8724
Fax: 202-872-6206

Sara Thurin-Rollin
Reporter
The Bureau of National Affairs, Inc.
1231 25th Street, NW
Washington, DC 20037
202-452-4584
Fax: 202-452-4150

Patrick Tracy
Vice President
American Portland Cement Alliance
1212 New York Avenue, NW
Suite 500
Washington, DC 20005
202-408-9494
Fax: 202-408-9392

Karl Traul
Director, Strategic
Regulatory Toxicology
Agricultural Research Division
American Cynmaid Company
P.O. Box 400
Princeton, NJ 08543-0400
609-799-0400
Fax: 609-275-3578

Peter Voytek
Executive Director
Halogenated Solvents
Industry Alliance
2001 L Street, NW - Suite 506A
Washington, DC 20036
202-775-0232
Fax: 202-833-0381

Ruth Weir
Technical Program Manager
Systems Applications International
101 Lucas Calley Road
San Rafael, CA 94903
415-507-7100
Fax: 415-507-7177

Anthony Wells
Medical Director
Owens Corning Canada
4100 Yonge Street
Willowdale, Ontario M2P 2B6
Canada
416-484-6760
Fax: 416-484-6761

John Whysner
Executive Secretary
Environmental Health &
Safety Council
American Health Foundation
One Dana Road
Valhalla, NY 10595
914-789-7137
Fax: 914-592-6317

John Wilkinson
Halogenated Solvents
Industry Alliance
2001 L Street - Suite 506A
Washington, DC 20036
202-775-0232
Fax: 202-833-0381

Richard Williams
Chief, Economics Branch
Center for Food Science &
Applied Nutrition
U.S. Food & Durg Administration
200 C Street, SW (HFF-726)
Washington, DC 20204
202-401-6088
Fax: 202-260-0794

Kelli Woodwick
Federal Regional Manager
Valent U.S.A. Corporation
1401 I Street, NW - Suite 305
Washington, DC 20005
202-872-4682
Fax: 202-872-4689

U.S. GOVERNMENT PRINTING OFFICE: 1995 - 650-006/00231