Preliminary scientific report of the EPA risk assessment guidelines for carcinogenicity, mutagenicity, chemical mixtures, developmental effects and exposure assessment

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

June 19, 1985

Hon. Lee M. Thomas
Administrator
U. S. Environmental Protection
Agency
401 M Street S. W.
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OFFICE OF
THE ADMINISTRATOR

Dear Mr. Thomas:

The Science Advisory Board has completed its preliminary scientific review, as requested, of the EPA Risk Assessment Guidelines for Carcinogenicity, Mutagenicity, Chemical Mixtures, Developmental Effects and Exposure Assessment. To carry out its review the Board's Executive Committee formed five Risk Assessment Guidelines' Review Groups consisting of scientists with expertise in the subject matter of each guideline. These groups met in public session on March 4 for a preliminary planning meeting and on April 22-23 to discuss and evaluate a number of technical issues with EPA staff as well as members of the public. The Executive Committee prescheduled its meeting for April 25-26 to expedite its evaluation of the Review Groups' draft reports and to enable you to receive the final SAB reports in a timely fashion. Enclosed are preliminary reports on each of the five guidelines. As agreed to by EPA staff, the chairs of each SAB Review Group will have the opportunity to see revisions to the guidelines to determine which of the SAB suggested changes were incorporated. If needed, the chairs may distribute the revised guidelines to all members of the Review Group. Following this second review of the revised guidelines, the chairmen will expeditiously prepare final reports.

The Risk Assessment Guidelines' Review Groups addressed two major issues in their respective reviews. These included the adequacy of the scientific rationale that identifies the need for guidelines and articulates the conceptual framework behind their development, and the adequacy of the Agency staff's interpretation of a number of technical issues associated with each guideline. The major SAB conclusions and recommendations for each guideline can be summarized as follows:

- The Carcinogenicity Guidelines Review Group advises that the proposed, updated guidelines for cancer are needed. Since the publication of the 1976 Interim Guidelines for Carcinogenicity, considerable change has occurred in both the underlying scientific data base and in the development of risk assessment methodologies. The proposed guidelines are reasonably complete in their current form. Two additional issues that need to be addressed include: 1) transplacental, multi-generational or total lifetime animal bioassays, and 2) sensitivity analysis of the quantitative estimate of potency. Regarding the Agency's interpretation of the scientific issues, EPA's proposed guidelines are generally consistent with the recently published Office of Science and Technology Policy principles for chemical carcinogens, and they address the important issues raised in the public comment period.

Contingent on the adoption of minor revisions outlined in the technical report prepared by the Review Group, the proposed guidelines are scientifically adequate for EPA staff to develop risk assessments in support of Agency decision making.

- The Mutagenicity Guidelines Review Group unanimously concurs that the proposed guidelines are based on an adequate scientific rationale as determined by the existing state of knowledge in this field. The guidelines represent a successful effort in articulating the background information necessary to develop a risk estimation approach for judging the potential human mutagenicity of a chemical. Such an appoach can be used to develop qualitative weight-of-evidence assessments and, in special cases, provides guidance to develop quantitative risk assessments. The Review Group recommends that an eight level rank ordering of studies be used in the weight-of-evidence determination of qualitative risk. The Group also provides the Agency with research recommendations that, if pursued, would supply EPA with needed and more precise tools for risk assessment.

- The Chemical Mixtures Review Group commends the EPA work group for developing a very good draft of rational guidelines for health risk assessment in this very complicated area of environmental health. These guidelines were published later than the others and EPA staff did not have time to incorporate changes based on public comments. Agency staff agreed to submit a revised draft for the panel's review prior to finalizing the guidelines. The principal scientific recommendations which the Review Group brings to your attention include:

  1. A need for revision of a summary table which describes the preferred approach to risk assessment for chemical mixtures. The table needs to be clarified and expanded to provide more options. In particular, there may be conditions in which the poor quality of data and absence of relevant information could lead to a "non-definable risk" outcome.

  2. Developing and incorporating a system to express the level of confidence associated with various steps in the risk assessment process. This might include a weight-of-evidence approach analagous to the classification system for carcinogens developed by the International Agency for Research on Cancer and would require development of a taxonomy of chemical mixtures. Sensitivity analysis is also recommended to assess the impact of various uncertainties on risk estimates.

  3. Because the scientific background of health effects of chemical mixtures is very broad and diverse, and at the same time full of critical gaps, there is a need for a separate document which in effect would be a technical support document for the guidelines. The study of interactions of chemicals in biological systems is a comparatively immature science. Progress in improving risk assessment will be unusually dependent upon progress in the science of interactions.

- The Developmental Effects Review Group concludes that, in general, the proposed guidelines are scientifically adequate and commensurate with the present state of the science. The field of developmental toxicology is, however, particularly weak with respect to quantitative assessment. The proposed guidelines could be improved in the section addressing the relationships of maternal toxicity in comparison to toxicity of the fetus. The basis for quantitative assessment also needs elaboration.

- The Exposure Assessment Review Group finds that the proposed guidelines provide a very good overview of the general principles to be followed in conducting exposure assessments and of the use of models to estimate exposures in the absence of reliable exposure data based on measurements. However, in their present state, they fail to sufficiently emphasize that exposure assessments based on reliable measurements of pollutant concentrations in relevant environmental media should take precedence over exposure estimates based on unvalidated models. In addition, they fail to provide guidance on the general principles to be followed in measuring pollutant concentrations in environmental media. EPA should prepare a supplementary guideline addressing this latter issue.

The Risk Assessment Guidelines' Review Groups also addressed and made recommendations on several generic issues relating to the Risk Assessment Guidelines. These include:

- The proposed guidelines provide a conceptual framework that is generally applicable to radioactive substances as well as to chemicals. However, it is recognized that differences exist in the physical and biological properties of these classes of pollutants as well as differences in their human health and environmental fate and effects. The Agency should consider whether to develop separate guidelines for radiation that recognize these similarities and differences and serve as the basis for radiation risk assessments.

- The development of Risk Assessment Guidelines suggests a number of areas for improving the scientific understanding of pollutant behavior and effects. The Review Groups have recommended a number of research needs to the Agency's attention. The Office of Research and Development should make use of these recommendations and use the guidelines' development process to enhance its research planning process.

- The Science Advisory Board concurs with the Agency's recommendation to periodically update the guidelines as additional scientific knowledge may warrant.

The Science Advisory Board recognizes the significance of the effort to develop Risk Assessment Guidelines and applauds the Agency for taking this initiative. When finalized, they should provide the basis for greater consistency in the development and utilization of risk assessments by all the program offices and should assist the Agency's senior managers in communicating complex scientific issues to the public. The Board appreciates the opportunity to provide its advice on the guidelines and will provide any additional review that is requested. An Agency response to the Board's advice is requested.

Sincerely,

Norton Nelson, Chairman
Science Advisory Board

REPORT BY THE SAB CARCINOGENICITY GUIDELINES REVIEW GROUP

INTRODUCTION

On April 22-23, 1985, the SAB Risk Assessment Guidelines' Review Group for Carcinogenicity met in public session to review a revised draft of the Agency's proposed Guidelines for Carcinogen Risk Assessment. EPA proposed the Guidelines in November, 1984. Public comments were received, and a revised draft that incorporated the Agency's response to these comments was made available to the Review Group. The comments below refer to this revised text and not to the November, 1984 draft document.

The Review Group advises that new guidelines for assessing cancer risks are needed. Since the publication of the Interim Guidelines in 1976,[1] both the underlying scientific information and risk assessment methods have changed considerably although basic principles remain the same.

The draft Guidelines are reasonably complete in their conceptual framework and are sound in their overall interpretation of the scientific issues. They are also generally consistent with the principles for chemical carcinogens issued by the Office of Science and Technology Policy (OSTP),[2] and address the important issues raised by the public comments. Contingent on the revisions outlined below, the draft Guidelines should provide reasonable guidance for EPA personnel to develop scientifically adequate based risk assessments in support of Agency decision making.

The Review Group identifies three kinds of recommendations including: (1) issues missing from the draft guidelines that should be added; (2) general advice that can be implemented by the Agency without further review; and (3) specific recommendations for wording changes. Most of the Review Group's comments are in the latter form and represent a carefully developed consensus of the reviewers. This specificity indicates the extent to which only minor changes are advised. The Review Group requests that EPA respond to this report and, if necessary, to particularly indicate what advice was not used together with a rationale for why it was not accepted.

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[1] U.S. Environmental Protection Agency, Health Risk and Economic Impact Assessments of Suspected Carcinogens: Interim Procedures and Guidelines Federal Register 41: (May 25, 1976), 21402-21405.

[2] Office of Science and Technology Policy, Chemical Carcinogens - A Review of the Science and its Associated Principles - February, 1985 Federal Register 50: (March 14, 1985), 10371-10442.

I. PROPOSALS FOR ADDITIONS TO THE GUIDELINES

The Review Group concludes that two additional issues need to be addressed in the guidelines before they are finalized. These include: (1) transplacental, multi-generational or total lifetime animal bioassays, and (2) sensitivity analysis of the quantitative estimate of potency. EPA staff should develop the wording of the section on transplacental, multi-generational or total lifetime bioassays. The Review Group has provided specific language to be added for sensitivity analysis of quantitative estimates. (See "Recommendations for Specific Wording Changes" p. 29, below.)

II. GENERAL COMMENTS

The Review Group advises that the Agency add a paragraph to the introduction that describes the general differences between the current version of the guidelines and the Interim Guidelines of 1976. The numbering of the major sections also should be revised, with the dose-response section as part II, the exposure section as part III, and the risk characterization section as part IV. The distinction between qualitative and quantitative assessment is implicit thoughout the document, but the introduction should explicitly define these terms. The references in the proposed guidelines to the Office of Science and Technology Policy principles need to define the relationship between the two documents more explicitly, that is, the OSTP document contains a general discussion of the scientific basis for risk assessment whereas the EPA document sets out practical guidelines for carrying out risk assessment.

The panel members proceeded through the revised draft guidelines on an issue by issue basis, first discussing an issue in detail and then testing the revised draft against the discussion. The panel believes that, in general, the guidelines adequately define the assumptions made in evaluating the scientific issues that are addressed. However, the Agency needs to distinguish recommendations based on scientific evidence from those based on science policy considerations. In essence, EPA's recommendations represent choices between competing scientific hypotheses for which the available data do not always permit a clear decision. The draft guidelines explain this distinction well in discussing the use of the "linearized multi-stage model" to develop plausible upper bound estimates of potency. The Review Group suggests a similiar approach for questions such as extrapolation between routes of administration or extrapolation between species (body weight versus surface area). The latter topic should refer to more recent information and make clear that consideration of more sensitive human subpopulations forms the rationale for selecting the most sensitive animal species for quantification purposes. The recommendations for extrapolation between routes of administration need to make the procedure more explicit.

The Review Group concurs with the Agency's stated positions on cancer promoters. The term "promoter" is operationally defined, and current bioassay procedures do not permit the designation of a chemical as exclusively a promoter or an initiator.

The Agency's senior policy officials should have sufficient flexibility to define various options in deciding whether to regulate specific compounds. Although the guidelines represent a logical input to establishing a policy response, they should not delimit the series of factors, both scientific and non-scientific, considered in regulatory decision making. Control of exposure, discussed in the guidelines, seems to the Review Group to constitute only one o a number of available options. In cases where data were inadequate to make a regulatory decision, the Agency could recommend further testing or exposure evaluation on a priority basis. (See page 6 of the revised draft.)

In developing the section on the elements of hazard identification the Review Group suggests that the guidelines draw the risk assessor's attention to a series of issues that will influence the interpretation of cancer risk. These include:

(1) Strength of the evidence
(2) Promotion or co-carcinogenesis
(3) Maximum tolerated dose
(4) Mouse liver tumors
(5) Benign tumors
(6) Statistical considerations
(7) Historical controls
(8) Negative data
(9) Positive data
(10) Interractions
(11) Variability in human response

Regarding the issue of less than lifetime exposure, the Review Group recommends that the Agency improve on the methods used in the guidelines to develop ranges of estimates. When using the multi-stage model, reference to the method of Crump and Howe will be useful. More generally, the method of Gaylor and Kodell is suggested. The document should describe alternative methods to deal with less than lifetime exposure.

In the description of the weight-of-the-evidence for epidemiological data, biological plausibility and temporal sequence should be mentioned as factors to be considered in the evaluation. Throughout the document the term "weight-of-the-evidence" should be used consistently, and reference to apparent synonyms that may confuse, such as "degree-of-evidence" or simply "evidence," should be deleted. The Review Group concurs with the overall weight-of-the evidence categories developed by the Agency, but we advise that the Agency should:

(1) not use letters tc represent the categories unless a descriptive paragraph on the substance is always used in conjunction;
(2) add a table to the appendix of the guidelines showing the suggested combined weight-of-the-evidence category for each possible permutation of categories of animal and human weights-of-evidence; and
(3) clarify that regulatory decisions should not be based on the classification system alone but will include consideration of factors such as potential human exposure.

Finally, the insertions added to the revised test, including the Review Group's recommendations, make the text awkward in places, and a final editorial revision for readability is recommended.

III. RECOMMENDATIONS FOR SPECIFIC WORDING CHANGES

[Insert on page 7, after line 4 as a new paragraph]

° A major theme of the approach being advocated for risk assessment is the use of a weight-of-the-evidence methodology. This is because inadequacies in our knowledge of carcinogenesis preclude advocating a step by step prescriptive "cook-book" approach applicable to all suspect carcinogens. Of necessity, the use of a weight-of-the-evidence approach places particular emphasis on the exercise of scientific judgment in reviewing and selecting information to be used in either the qualitative or quantitative elements of the carcinogen risk assessment process. In selecting information for inclusion in the process, priority will be given to information validated through replication and peer review. Special weight will be given to human data when they are available and adequate for purposes of risk assessment. Generally, however, such data are not adequate and it is necessary to rely on experimental data. When data are selected for use in a risk assessment from among multiple data sources, the basis for selection or exclusion of the data will be explicitly stated.

[Page 8, Section II.B.2., insert into line 2]

... "that argue for <u>or against</u> the prediction ...,

[Page 8, Section II.B.3., last paragraph, line 4, change to]

... molecular interactions, <u>biologically effective dose</u>, and transport in, fate in, <u>storage</u> in and excretion from the body, as well as ... metabolism should be discussed <u>and critically evaluated</u>.

[Insert on, page 9 before "6. Long Term Animal Studies" (add the following)]

° The implications of information presented in this section regarding shape of the dose-response relationship, biologically effective dose, saturation effects, immune system effects, short-term test results, species differences, etc., should be summarized so as to facilitate the interpretation of data from long-term animal studies.

[Page 9, Section II.B.4., first paragraph, line 3, add]

° These should include interactions with other chemicals or agents and with lifestyle factors, where applicable. Storage in the body and possible recycling should also be considered.

[Page 9, Section II.B.6., and forward throughout the text, where appropriate, begin the subsections of the Guidelines by stating]

° "This section of an assessment should include ....."

[Page 9, Paragraph 3, Line 3. add:]

... However, lack of positive results in short term tests for genetic toxicity do not, by themselves, provide a basis for discounting positive results in animal bioassays.

[Page 10, Paragraph 1, line 9, delete]

... "of the same morphologic type."

[Page 10, Paragraph 1, line 11, add]

... malignant tumors, in most cases the evidence will be considered...

[Page 10, last paragraph, 1st sentence, at the end of the sentence add references to]

° (NTP, 1984) (IARC preamble).

[Page 11, paragraph 1, line 14, change to]

... high exposures alter tumor responses by mechanisms that may be ...

[Page 11, paragraph 1, line 15, changes to]

... lower exposures should be ...

[Page 11, paragraph 2, line 4, change to]

... and implantation site sarcomas.

[Page 12, paragraph 2, line 1, change to]

° To evaluate carcinogenicity, the primary comparison is tumor response in dosed animals as compared with that in contemporary matched control animals. Historic control data are often valuable, however, and ...

[Page 12, 2nd paragraph, end of last sentence, add reference to]

° (NTP, 1984)

[Page 12, paragraph 2, line 8, change to]

... group may become questionable

[Page 12, paragraph 2, line 10 change to]

... an unusual background incidence (NTP, 1984).

[Page 12, last paragraph, line 5, add]

° (Haseman, 1984)

[Page 13, replacing lines 3 & 4]

... classification could be changed on a case-by-case basis to "limited," if warranted by the available information on each specfic substance. Factors to be taken into account in this determination could include: the occurrence of tumors ...

[Page 13, paragraph 1, line 8 delete]

"showing no evidence of metastases or invasion:"

[Page 13, paragraph 1, line 9, replace with]

... tumors:

[Delete]

"the occurrence of excess tumors only as a single sex.

[Page 13, paragraph 2, add at the beginning]

° All bioassay data are to be considered in the evaluation of carcinogenicity.

[Page 13, paragraph 2, line 3, delete]

"... that are essentially identical in all other respects to a positive study ..."

[Page 14, Section II, B.7., paragraph 2, line 6, change to]

... causes of morbidity and death, and the power to detect an effect. The power of studies should be included in the assessment.

[Page 15, 2nd paragraph, line 5. change to]

..."available evidence including exposure data."

[Page 16, Add]

... Category F - no data

[Page 17, Add at bottom]

... (5) no data

[Page 18, Section II. D., paragraph 2, line 9, restore]

Groups D and E generally would not have ...

[Page 20, paragraph 1, line 6, change to]

... uncertainty, may be useful, for example, in setting regulatory priorities and for evaluating ...

[Page 21, Section III. A.1., paragraph 1, line 3 change to]

... to the scientists doing the ...

[Page 21, Section III. A.1., paragraph 2, line 4, add at the end]

However, both estimates should be presented.

[Page 21, paragraph 2, line 15, change to]

... human sensitivity may be more or less than the most ...

[Page 23, paragraph 2, line 16: Add]

... "mechanisms of the carcinogenesis process are largely unknown and data are generally limited.....

[Page 23, paragraph 2, line 19, change to]

... the same carcinogenic processes ...

[Page 24, paragraph 1, line 9, change to]

In the absence of information to the contrary ... employed. Where appropriate, the results of..."

[Page 24, paragraph 2, line 1, replace first two sentences (The remainder of the 2nd paragraph, beginning "In certain cases..." becomes a new paragraph)]

° It should be emphasized that the linearized multi-stage model leads to a plausible upper limit to the risk that is consistent with widely accepted mechanisms of carcinogenesis. However, such an estimate does not necessarily give a realistic prediction of the risk. The true value of the risk is uncertain, and for many substances the lower bound estimate of risk is zero. The Agency's procedures lead to a range of risk, defined by the upper limit

estimate from the linearized multi-stage model and a lower limit, which should be explicitly stated. An established procedure that is applicable to a variety of substances does not yet exist for making most likely or best estimates of risk within the range of uncertainty defined by the upper and lower limit estimates. However, on a case-by-case basis where the data and procedures are available, the Agency will strive to provide most likely or best estimates of risk for use in risk management. This will be most feasible when human data are available and when exposures are in the dose range of the data.

[Page 26, paragraph 1: Add]

... Regardless of the classification of a carcinogen, EPA should evaluate the available data on human and environmental exposure.

[Page 26, line 3 from bottom, change to]

... from all relevant sources of exposure <u>including multiple avenues of intake</u> from the same source.

[Page 26, last sentence]

....and modeling. The data and methods by which doses to the target organ are calculated should be described and critically evaluated.

[Page 27, paragraph 1, line 6, change to]

... recommended as <u>an</u> appropriate ...

[Page 27, paragraph 2, line 6, add to the end of paragraph]

Subpopulations with heightened susceptibility (either because of exposure or predisposition) should, when possible, be identified.

[Page 29, change the current 3 to 4, and add a new 3 called Host Factors. Genetic, sex, health or age related factors known or believed to influence susceptibility should also be taken into account.]

[Page 29, Section III.C.3., after line 8, add]

° In presenting quantitative estimates of risk and where sufficient data are available, it will be appropriate to provide the results of sensitivity analyses of the various selected models used to calculate risk. Such an analysis requires an explicit statement of the assumptions and selected parameters used in the models and will aid in identifying the influence of changes in the assumptions and parameters. This approach clarifies those assumptions and parameters that are most significant in influencing the final risk estimate values.

[Page 32: footnote: delete]

... life-threatening benign tumors.

[Page 35, line 16, change to]

... used for agent(s) with equivocal or inadequate human and animal evidence of carcinogenicity. Inadequate animal evidence may result from animal tests that are technically flawed or when there is a single negative animal bioassay.

[Page 35, line 18, change to]

Group E - No Positive Evidence of ...

Group F - No data available

The Review Group found EPA's proposed Guidelines for Mutagenicity Risk Assessment to be well researched and commends the staff who prepared them for doing a thorough job in presenting the scientific issues associated with assessing the risk of environmental mutagens, discussing the approaches for qualitative and quantitative risk estimation and in addressing the major areas of scientific concern and uncertainty.

Although it was not a major area of disagreement, the Review Group has prepared, for Agency consideration, a rank ordering of studies to be used in the weight-of-evidence determination of qualitative risk. The proposed ranking, in numerical order, deals with test attributes that EPA should use to define the levels of evidence relating to human mutagenicity induced by a chemcial(s). These eight ranking levels include:

1. Positive data derived from human germ-cell mutagenicity studies, when available, will constitute the highest level of evidence for human mutagenicity.

2. Valid positive results from studies on heritable mutational events (of any kind) in mammalian germ cells.

3. Valid positive results from mammalian germ-cell chromosome aberration studies that do not include an intergeneration test.

4. Sufficient evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity test results from two assay systems, at least one of which is mammalian (in vitro or in vivo). The positive results may both be for gene mutations or both for chromosome aberrations; if one is for gene mutations and the other for chromosome aberrations, both must be from mammalian systems.

5. Suggestive evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity evidence from two assay systems as described under 4 above. Alternatively, positive mutagenicity evidence of less strength than defined under 4 above, when combined with sufficient evidence for a chemical's interaction with mammalian germ cells.

6. Positive mutagenicity test results of less strength than defined under 4 above, combined with sugestive evidence for a chemical's interaction with mammalian germ cells.

7. Although definitive proof of nonmutagenicity is not possible, a chemical could be classified operationally as not a human germ-cell mutagen, if it gives valid negative test results for all endpoints of concern that are enumerated in the guidelines.

8. Inadequate evidence bearing on either mutagenicity or chemical interaction with mammalian germ cells.

In addition to this ranking system for evaluating evidence for mutugenicity, the Review Group made several recommendations relating to other aspects of the guidelines. These include:

- EPA should include additional references within the guidelines pertinent to established and accepted genetic-risk estimation procedures that specifically deal with the characterization of the human disease burden introduced by an increase in mutation.

- The Agency should modify the section on testing systems to more specifically detail existing mammalian germ cell tests and provide a brief discussion of their strengths and weaknesses and the limited availability of data for certain tests.

- The quantitative risk section should place greater emphasis on data derived from exposure, exposure rate and or other regimens that most closely simulate the human experience.

The Review Group recognizes a number of research areas that, if pursued diligently, could provide the Agency with needed tools to assess human genetic risk more adequately. Although not exhaustive, the following issues deserve attention:

1. More experimental work on mammalian oocyte response to mutagens, in a variety of experimental mammalian species.

2. Enhancing the attempts to correlate mammalian germ and somatic cell mutagenic data with equivalent human somatic cell data in an effort to predict induced human germ risk. These studies should utilize some well-defined mutagens.

3. Further studies employing dominant mutant phenotypes (e.g., skeletal and cataract) that could be used in both sexes and between different mammalian species. Such studies would improve the confidence in interspecies extrapolation to man. Moreover, additional work needs to be done to characterize the mutation component of these genetic endpoints.

4. Continued development of aneuploidy technology in germ cells of both sexes and particularly in mammals with an aim toward improving quantitative risk estimation.

5. Studies that will better define the baseline incidence of human genetic disease and the mutational components associated with the various subcategories of disease determined by various genetic mechanisms.

6. More experimental studies on varying exposure regimes and rates of exposure are needed in eukargate test systems in order to provide needed models for extrapolation to low doses.

The Review Group concludes that the scientific adequacy of the proposed Guidelines for Mutagenicity Risk Assessment accurately reflect the state of the art of this field. We have presented the Agency staff with a series of minor changes in the document that we believe will improve the clarity and general intent of the guidelines. Since these are noted in the transcript of the meeting, we do not intend to specify a line-by-line editing but note that the staff is in general agreement with these changes.

REPORT OF THE CHEMICAL MIXTURES GUIDELINES REVIEW GROUP

Introduction

The problem of assessing health risks of exposure to chemical mixtures is a very important issue for the Agency. In terms of public concern, it is one of the highest priorities in public health, highlighted by the reactions of communities impacted by hazardous waste dump sites.

Most environmental exposures are to mixtures rather than to single chemicals. In a strict sense, it is correct to think of all exposures as exposures to complex mixtures of chemical and physical factors, variable with time and interacting in complex ways. Focusing regulatory attention on single chemicals results from many practical considerations but tends to oversimplify the problem of assessing health risks.

This is the Agency's first attempt to develop guidelines for risk assessment of chemical mixtures. It is a good first effort, but should be considered only as a step in the evolution of guidelines which should be revised and improved as more scientific information on interactions becomes available and as risk assessors evaluate their experience periodically.

The proposed guidelines submitted to the Review Group were released for public comment on January 9, 1985. An internal Agency working group has reviewed the public comments submitted by March 11, 1985, but it has not had time to incorporate changes in a revised set of guidelines. EPA staff will consider the comments of the present Review Group and of the public for preparation of a new draft. The Review Group expects that the revised document will be submitted for its review.

Conceptual Framework of the Guidelines

The Review Group considers the conceptual framework of the current guidelines to be scientifically sound. It notes that the conceptual issues on which these guidelines are based are very different from those of other risk assessment guidelines, for example, those which address health effects such as cancer.

The Review Group also recognizes that there is a relatively meager data base on the health effects of chemical mixtures and little experience in preparing these kinds of risk assessments. Scientific evaluation of potentially adverse health effects of chemical mixtures is an area of toxicology that has not undergone extensive research and testing either in humans or in laboratory animals. Furthermore, such research and testing is complicated by the number and variety of different chemical mixtures encountered, either man-made or those that occur naturally. In addition, when interactions of more than two chemicals are studied systematically, the complexity of experimental design is increased and the size of the project and the costs can increase enormously.

Although not a matter of conceptual framework, the guidelines would be better understood and more easily used by risk assessors and the public if they were substantially rewritten. Information on potential uses of the guidelines would be helpful to individuals outside the Agency. Numerous reviewers have noted the absence of any definition of chemical mixtures. A few examples are given, but no limitation is placed on what might constitute a complex mixture. There is also no recognition of the temporal component of exposures to mixtures. In several parts of the document more care is needed in precise definition of terminology.

Recommendation

The current proposed guidelines should be revised addressing comments received at and since the March 4, 1985 preliminary meeting of the Review Group as well as those received from the April 22-23, 1985 meeting. This redraft should be reviewed by mail by the Review Group at which time the need for further review will be considered, including the possibility of resubmission for public comments.

Scientific Issues

1. Issues relating to the guidelines' summary in Table 1 (page 1171)

The proposed guidelines recognize that the amount and types of data available on a chemical mixture may vary considerably. The recommendation is to emphasize "flexibility, judgment and clear articulation of the assumptions and limitation in any risk assessment." EPA staff have incorporated a table summarizing the proposed approach to chemical mixtures.

The Review Group found this tabular summary helpful but has several suggestions intended to increase its utility. These include:

- The concepts in Table 1 should be presented in flow chart form such that the decisions to be made at each branch point are illustrated, the consequences of that decision made explicit and, if possible, the data needs articulated. The table format does not allow for recycle loops or multiple options if appropriate. This revision in format could also reflect the differences in the quality of available information where one set of decisions are clearly data-based and another are highly inferential.

- In the text or in an appendix, EPA should provide illustrative examples of how the guidelines would be used. These examples would be drawn from actual cases performed by the Agency or would be simulations designed to elucidate the procedure. It has been noted elsewhere in this report that the guidelines contain too few examples. This table (or chart), which for some readers will be the only thing they read, would benefit from such an illustration.

- The Review Group found that not all important outcomes were accounted for in the table. It recommends that the flow chart or comparable device be expanded to include additional options. For example, where more than one outcome is of importance to the risk manager, the interaction of such outcomes should be indicated. This interaction could involve carcinogenic and systemic toxicity endpoints or mutagenic and developmental effects.

In the evaluation of "sufficient similarity," there is the need for the guidelines to recognize that this concept could be defined in terms of composition (e.g. an homologous series of hydrocarbons) or in terms of end-effects (e.g. a series of Central Nervous System depressants such as alcohols, ketones and simple esters).

The importance of exposure data in identifying and quantifying risk is not integrated into the proposed scheme. Such data are needed for the proper use of Step 3 which deals with indices of acceptable exposure.

Most importantly, there should be a branch in the decision logic which leads to a "non-definable risk" outcome. The Review Group believes that conditions can exist in which there are no toxicity data available on the chemical mixtures; there is no "sufficiently similar" mixture which has been studied; the number of unidentified components is large and/or the amount of data on the few identifiable components is small. In such instances, hazard identification, the acknowledged first step in risk assessment, is not possible. Consequently, the decision process should move to a "non-definable risk" outcome. The alternative is an assessment with such wide uncertainty bands as to be meaningless or misleading.

2. Greater emphasis on levels of confidence in risk assessments

The scientific basis for estimating the risks of chemical mixtures is highly variable depending upon the type of mixture, the complexity of the mixture, and data availability. A risk assessment based upon bioassay data for the mixture in question, for example, probably has a much higher degree of confidence associated with it than does a risk assessment based upon the toxicity of some of the components of a poorly-characterized mixture. There is a need to express the degree of confidence to be associated with various risk assessments of chemical mixtures. Accordingly, the Review Group recommends that the guidelines be revised to develop and incorporate a system to express the level of confidence associated with a risk assessment. Such a system might, for example, be analogous to the IARC classification system for carcinogens, which summarizes the weight of evidence for carcinogenicity of a chemical. The development of such a system will probably require a taxonomy of chemical mixtures. Such a system should take into account the nature of risk associated with the components of the mixture (all carcinogens, all toxicants, both present), the complexity of the mixture (well characterized, composed of few or many chemicals, poorly characterized), and data availability (available for the same or similar mixtures, available for some or all components, and knowledge of potential interactions).

The Review Group also notes that there are more assumptions and uncertainties associated with the risk assessment of chemical mixtures than of single chemicals. The mixtures may be poorly characterized; in some cases, only some of the components may be identified or the mixture may be defined to be similar to another one. Little information is probably known about potential antagonistic or synergistic reactions, and often this information may be qualitative in nature. Theories and models developed for single chemicals may not be appropriately transferred to chemical mixtures; for example, the extrapolation of high dose response data on a mixture having carcinogenic properties may not be the same as for single chemicals; this is also true for interspecies extrapolations, and any interactive mechanisms which may be present may not be constant across all dose levels. The Review Group urges that these uncertainties be clearly articulated and that sensitivity analyses be undertaken, where appropriate, to reflect the likely impact of some of this uncertainty on the risk estimates. The sensitivity analyses should reflect differences in ways to address the risk of a chemical mixture (e.g., whether it is based on the toxicity of a "similar mixture" or on knowledge of the toxicity of constituent components), differences in the application of the additivity assumption in calculating the hazard index (different groupings of mechanisms), and differences due to interaction assumptions that may be

based upon qualitative or suggestive data. Variations inherent in single chemical risk assessments should also be covered by the sensitivity analyses; these variations include the use of alternative data sets, extrapolation from different species, use of alternative pathology results, use of confidence intervals and alternative exposure levels.

3. Need for a technical support document

The technical and scientific background from which these guidelines must draw their validity is so broad and varied that it can't reasonably be summarized within the framework of a brief set of guidelines. Numerous reviewers, including the Review Group, believe that the guidelines would greatly benefit by the preparation of a technical support document. Such a document, as a minimum, would describe the biologic principles of toxicologic interactions associated with multiple chemical exposures; would identify alternative approaches, the assumptions behind these approaches and the impacts of violating the assumptions; and would use illustrative examples liberally throughout the document. The support document would also supply the technical references which are somewhat deficient in the guidelines. The Review Group suggests the following as some of the topics that might be included in such a technical document (it is assumed that the EPA working group would use this as a guide, and would undoubtedly add other topics of its own):

- Summaries of toxicity studies of chemical mixtures, including their relevance to the theoretical basis of interactions.
- Definition and basis of dose additivity models, with illustrative examples.
- Similar delineation of response additivity, with examples.
- Definition and examples of risk additivity.
- How to quantify uncertainties.
- How to deal with mixtures that contain both carcinogenic and systemic toxicants that are non-carcinogenic.
- Role, importance, need for mechanistic data on toxicologic interactions.
- Effect of temporal sequence on additivity models.
- Recommendations for methods of testing mixtures.
- How to test mathematical models for plausibility.
- How to deal with the Maximum Tolerated Dose (MTD) concept in carcinogen bioassay as it deals with mixtures since no one component may be present at MTD.

- o Is there a theoretical or practical limit to the number of agents in a dose additive model?
- o Role of matrix sensitivity—toxicity of an agent may be a function of other agents being present.
- o Criteria and methods for evaluation of data quality.
- o Relationship between mechanisms of interactions and mechanisms of toxicity.
- o Research needs

Other Issues

1. Identification of research needs

Although the toxicity of chemical mixtures has been recognized for decades as an important area for toxicologic research, there has been little emphasis on this area until recently. Consequently, the existence of large gaps in available information is not surprising. The Review Group believes that an important mechanism for identifying critical research needs is inherent in the process of carrying out risk assessments. The Office of Research and Development should ensure that there is an effective linkage with the research planning process to take full advantage of these opportunities.

The preparation of the technical support document will also identify many research needs, which likewise should be made available and utilized in the research planning process.

2. Use of case-by-case approach.

As indicated in the guidelines and elsewhere in this report, the basis of scientific information is very meager for quantitative risk assessment for exposure to multi-component mixtures, with the exception of a few complex single source emissions or products (such as coke-oven exhaust, gasoline, PCBs). Consequently it is appropriate, as the guidelines suggest, to be very flexible in approaches to risk assessment. The Review Group suggests that risk assessments of chemical mixtures be done on a case-by-case basis, until a substantial background of experience is built up in this area.

3. "Enshrining the uncertainty"

The guidelines themselves, and to a greater extent this Review Group report, have emphasized the need to specify the level of confidence (or degrees of uncertainty) in various steps of the risk assessment. The Review Group believes these estimates should not only be a component of the risk assessment but should be carried forward through all steps in the risk management process and be made a part of releases of information to the public. The Review Group indentifies the objective of this process to be "enshrining the uncertainty."

Overall scientific adequacy of the Risk Assessment Guidelines for Chemical Mixtures.

The Review Group believes it would be inappropriate to state a conclusion on scientific adequacy at this time, inasmuch as the draft guidelines are in the process of revision. The document was on a different schedule by several weeks, and the closure of public comments did not occur until March 11, 1985. The EPA working group is already preparing a revised draft, based on the public comments, Agency comments, and the SAB meetings of March 4 and April 22-23. EPA staff anticipate completing the revision within approximately 30 days and has asked the Review Group to consider the revised draft. This will be done by mail and by a conference call; another meeting will be held if deemed necessary after the conference call.

The Review Group believes that present operational guidelines for chemical mixtures should continue to be used as interim guidelines.

The technical support document should be submitted to the usual peer review process for technical documents and should be submitted to the SAB for review. The SAB should evaluate the document in terms of its suitability as support for the chemical mixtures guidelines, and should recommend whether the draft support document should be made available for public comment.

REPORT OF THE DEVELOPMENTAL EFFECTS GUIDELINES REVIEW GROUP

Scientific Adequacy of the Guidelines

The Review Group concludes that, in general, the proposed guidelines are scientifically adequate and commensurate with the present state of the science. However, the field of developmental toxicology is particularly weak with respect to quantitative assessments. The guidelines could be improved by revisions in the section relating to the relationships of the maternal toxicity in comparison to toxicity for the fetus. The bases for quantitative assessment also require elaboration. The Review Group requests responses from the Agency on the specific points raised and the opportunity to review a revised draft at which time we will render a final opinion.

General Conclusions

The proposed Guidelines for the Health Assessment of Suspect Developmental Toxicants are generally well written and appropriately express the kinds of actions which are possible, given the present state of the art. Developmental toxicity studies have largely addressed qualitative responses, and the guidelines reflect this situation. Most of the testing methodologies employed at present are not as readily adaptable to quantitative assessments, especially with respect to chronic exposures.

Specific Issues

1. Integration With Other Guidelines

The Review Group understands that the guidelines for reproductive effects that are not maternally mediated are still under development. It is also clear that many instances will occur in which it will be difficult to differentiate between paternally mediated effects, effects originating during fertilization, maternally mediated reproductive effects and direct effects on the fetus. As EPA develops these additional guidelines for risk assessment it should integrate them with the existing guidelines as they evolve.

2. Definitions

The Review Group briefly discussed definitions used in the proposed guidelines and concurred that the concept of "functional developmental toxicology" was useful. However, it also noted that the well-established concept of "teratogenicity" appeared to be subsumed under other definitions and concepts in a number of instances. EPA needs to make distinctions in the definitions and use of these concepts.

3. Qualitative Assessments

The possible number of adverse effects in reproductive toxicology, in contrast to the possible number of outcomes in carcinogenicity testing, is very large. Consequently, the probability of missing an adverse effect, because it was not anticipated in the experimental design, is a much more likely event. This fact introduces complexities into the assessment of developmental toxicity that EPA should keep in mind.

If the available animal data indicate that a substance disrupts development only at maternally toxic doses, and if exposure potential may also include the maternal toxic dose range, then the substance merits careful scrutiny and is a possible candidate for additional study.

In evaluating dose-related effects observed in maternal and developing organisms (at any dose used), it is important to apply judgment as to the comparative nature and severity of these effects. Moreover, effects in the developing organism in the presence of maternal effects should not necessarily be considered secondary effects or of lesser significance in evaluating developmental toxicity.

The proposed guidelines emphasize that the responses in the most appropriate and/or sensitive species should be used in risk assessment. The Review Group suggests that the most appropriate species be determined on the basis of metabolic and pharmacokinetic characteristics with direct bearing on the toxic mechanism in the experimental organism in comparison to humans.

EPA should evaluate functional tests in assessing developmental toxicity on the basis of sensitivity of such tests to subtle toxic effects, the recognition that functional tests may assist in interpreting the biological significance of other effects of exposures, and the fact that data obtained from human populations have sometimes indicated functional deficits. For example, behavioral testing in animals may also be useful in assessing questions of toxicity to the nervous system.

The Review Group expresses concern about the use of screening tests for developmental toxicity. It endorses the use of single high dose screening studies for the purpose of prioritization (as developed by Chwernov), with reservations. Panel members share the concern of several previous commenters that materials found to be positive in this screening test might be permanently labelled as "teratogenic" by the public at large, a label which we consider to be possibly premature in some instances since the test is likely to produce a relatively high number of false positives. Although we believe that it is desirable that screening tests produce very few false negative responses, and thus are bound to produce false positive responses, the tendency to place immediate labels on the positive responders is unfortunate and unjustified in some instances.

The Review Group also considered the possible utility of structure-activity relationships in screening new chemicals for possible developmental effects. Structure-activity relationships, although potentially useful, are not sufficiently advanced at this time to be generally useful even for preliminary assessments, with the possible exception of preliminary assessments of hormone analogs.

4. Quantitative Assessments

On theoretical grounds, in most cases a threshold should exist for developmental effects in terms of the dose required to elicit toxicity. However, there is not a sufficient basis to rule out the possibility that non-threshold models may be more appropriate for some endpoints of certain toxicants.

It is important to recognize that the No-Observed-Effect-Level (NOEL), No-Observed-Adverse-Effect-Level (NOAEL) and Lowest-Observed-Effect-Level (LOEL) approaches attempt to approximate an apparent threshold region that incorporate judgment as part of the quantitative approach. However, the presence or absence of a threshold is, at present, almost impossible to ascertain, and that an exact threshold cannot be readily determined by mathematical inference. The mere existence of an NOEL neither proves nor disproves the existence of a real threshold. An experimentally determined NOEL is not necessarily at or below a threshold dose and, in that context, it is important to examine the quantitative relationships of NOEL dose rates to dose rates that result in effects. The examination of the effects needs to take the type of severity of the effect into account including the dose rates at which they are elicited. The application of a safety factor or an uncertainty factor to an NOEL may still result in a residual risk.

In some instances it may be necessary to conduct a reanalysis of experimental data to determine whether the conclusions drawn by the authors of a study were valid, especially when the original types of statistical analyses seem to have been inappropriate, or when the reported statistical outcomes do not seem to be supported by the data.

The Review Group considered whether EPA should introduce a weighting factor into the range of adverse outcomes that could result from exposure to a developmental toxin. The consensus opinion was that the state of the science was not sufficiently developed to enable a determination of the relative importance of structural abnormalities, altered growth, functional deficiencies, and intrauterine death; the considerable uncertainties in extrapolating from one such effect to another, as well as from species to species for a given effect, was also noted. For human data, such determinations extend beyond the area of risk assessment into the risk management area. The question of malformations versus anatomic variations was also discussed. The Review Group believes that, although the significance of anatomic variations is at present not well understood, a dose related increase in their incidence should be taken into account in the risk assessment process.

REPORT OF THE SAB EXPOSURE ASSESSMENT GUIDELINES REVIEW GROUP

The proposed Guidelines for Exposure Assessment provide a very good statement on the general principles of exposure assessment and logical procedures to follow in the absence of reliable measurement data on exposure. Some specific comments which relate to the discussion on uncertainty are offered in a later section of this review and should be considered in the revisions and corrections that were given to EPA staff during the course of the review.

Despite the generally satisfactory conditions of the material included within the proposed guidelines, the Review Group concludes that it is unsatisfactory to entitle them as the EPA's "Guidelines for Exposure Assessment" because they give virtually no guidance on the uses of environmental measurements for exposure assessment. Some of the EPA program offices make extensive usage of measurement data in their exposure assessments, and quite properly so. Agency-wide guidelines should certainly acknowledge such usage and encourage more of it. The Review Group was unanimous in concluding that direct measurements of concentrations of pollutants in air, water, food, and soil, made with suitable sampling protocols and quality assurance practices, usually provide better indices of human exposure than theoretical models. A secondary benefit in the use of this approach to exposure assessment is that accumulated data can provide a basis for the validation of exposure models.

The proposed guidelines appear to have been written from the perspective that exposure assessment should depend primarily on models, supplemented when possible by measurements of the characteristics and strengths of pollutant sources such as stacks, discharge pipes, fugitive industrial emissions, and waste dumps. They give virtually no recognition to more directly relevant environmental media at the receptors. Specifically, the guidelines state (page 46307) that "The analysis of monitoring data should be considered a complement to environmental pathway and fate analysis..." They devote space to a general discussion of environmental fate, transport and transformation, and identification of principal pathways of exposure. However, not until the last sentence on Monitoring (page 46308) is an acknowledgement made that "Reliable, analytically determined values should be given precedence over estimated values whenever significant discrepancies are found" (between model and measurement data). The Review Group believes that measurements provide the best basis for exposure assessment, and that modeling should be used only when there are too limited numbers and/or inaccuracies in available measurements.

The Review Group unanimously concludes that the guidelines will only be partially complete until they are expanded to include a whole new section on the general principles of the measurement of pollutant concentrations in the various environmental media. Furthermore, the preface to the existing proposed guidelines should indicate that environmental measurements, whenever feasible should have precedence over estimates based on theoretical or empirical models. Where a limited amount of good environmental measurement data are available and need to be expanded with modelled exposures, the measurements provide a means of guiding the selections of model input parameters which can give a greater degree of confidence in the model predictions. The guidelines should also address the limitations of environmental concentration data for exposure assessment.

A section should be added which delineates errors encountered such as the representativeness of the samples, sampling error, laboratory analysis errors, and data manipulation errors. It should also discuss the differences between precision and accuracy.

The supporting documentation for the proposed guidelines now includes a background paper using TCDD as a model for exposure assessment. This provides a good example of how one can proceed to make an exposure assessment in the absence of relevant data. The documentation for the final guidelines would benefit from the inclusion of two other examples as well. One should be for a pollutant for which a relative wealth of environmental exposure data are available, such as carbon monoxide or lead. Another should be for pollutant for which a limited amount of data are available, e.g., benzol or arsenic.

The proposed guidelines have not specified the form of the output to be generated from the exposure assessment. We recommend that a specific form of the output be proposed, such as an estimated exposure distribution, specific of each target population, supplemented by appropriate indications of the uncertainty (e.g., confidence limits), for the estimated distribution function.

When combining estimated exposures across various scenarios, the association or correlation among the various components needs to be addressed.

When dealing with synergistic responses in the combined risk assessment context, the association or correlation among the agents needs to be addressed.

In summary, the Review Group finds that the proposed guidelines provide a very good overview of general principles to be followed in measuring pollutant concentrations in environmental media. However, in their present state, they fail to sufficiently emphasize that exposure assessments based on reliable measurements of pollutant concentrations in environmental media should take precedence over exposure estimates based on unvalidated models. In addition, they fail to provide guidance on the general principles to be followed in measuring pollutant concentrations in environmental media. These critical deficiencies need to be properly addressed before they can be recommended for approval as Agency-wide Guidelines for Exposure Assessment. At the same time, Agency staff should proceed to finalize those sections of the guidelines that state general principles of exposure assessment and procedures to follow in the absence of measurement data, following further consultation with the Review Group.

In discussing the report of the Review Group the SAB Executive Committee, by majority vote, further recommended that: 1) the preface of the Guidelines be revised to emphasize that direct measurements, whenever feasible, have procedence over estimates based on unvalidated models as the basis for the Agency's exposure assessments; 2) the revised guidelines, which should include the new preface and the corrections resulting from the Review Group and public comments, be retitled to indicate that it represents general guidance and procedures to be followed when direct measurements are not feasible, and to indicate that they are not overall guidelines for exposure assessment; and 3) that the Agency commit itself to the preparation, on a priority basis, to the preparation of a guidelines document on the performance of exposure assessments based in whole, or in part, on direct measurements of pollutant concentrations in environmental media.

Specific Comments on Uncertainty

1. We commend Dr. Whitmore's work on the uncertainty analysis which is utilized in the proposed guidelines. The analysis is useful where environmental measurements are not available or feasible, and exposures and exposure distributions need to be assessed using a theoretical model.

2. An important component of uncertainty that is not sufficiently addressed is uncertainty about the form of the model, i.e., systematic error or bias arising from the use of a model. When environmental measurements are available, the validation of the model can be used to determine the presence and magnitude of systematic errors. When exposure measurements are not available, some subjective judgment will be needed.

3. Another important component of uncertainty is the random error not predicted by the model, assuming that the model predicts the expected exposure under the assumed input variables, or some other summaries of the conditional exposure distribution (conditioned on the assumed input variables), leaving random components unexplained. It is important that this component of variation be included in the assessment of the distribution of exposures across the members in the target population.

4. It is important to impose probabilitic interpretations on the uncertainty assessment. One specific instance where this is lacking is the consideration of the range of an input variable. The range appears to be interpreted in an absolute sense: all members of the target population are expected to fall inside the range. Such an absolute range is either impossible to assess, or too wide to serve any useful purpose. It will be more useful to impose a probabilistic interpretation on the ranges. (For example, ranges in which 90% of the cases are expected to fall.)

5. The enhanced sensitivity analysis is not clearly presented. It should be emphasized that the true distribution of the input variable is likely to be less variable than the uniform distribution assumed in this analysis, and the exposure distribution imputed from this analysis will show more variability than the true exposure distribution. It should, therefore, be viewed as a conservative estimate (overestimate) of the prevelance in the upper range of exposures.

6. The sensitivity analyses should be used as screening tools to identify the input variables which require further assessment.

7. Since it is likely that certain subjective assessments will be used, either in the form of expert judgements or range-finding calculations, a review of the techniques that can be used to reach the best subjective assessments from individual experts also needs to be addressed. When limited environmental measurement data are available, the issue on combining subjective assessments and empirical measurements needs also to be addressed.

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