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# Guidelines for the Health Risk Assessment of Chemical Mixtures

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

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This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Note: This document represents the final guidelines. A number of editorial corrections have been made during conversion and subsequent proofreading to ensure the accuracy of this publication.

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**GUIDELINES FOR THE HEALTH RISK ASSESSMENT OF CHEMICAL MIXTURES**
**[FRL-2984-2]**

**AGENCY:** U.S. Environmental Protection Agency (EPA).

**ACTION:** Final Guidelines for the Health Risk Assessment of Chemical Mixtures.

**SUMMARY:** The U.S. Environmental Protection Agency is today issuing five guidelines for assessing the health risks of environmental pollutants. These are:

Guidelines for Carcinogen Risk Assessment
Guidelines for Estimating Exposures
Guidelines for Mutagenicity Risk Assessment
Guidelines for the Health Assessment of Suspect Developmental Toxicants
Guidelines for the Health Risk Assessment of Chemical Mixtures

This notice contains the Guidelines for the Health Risk Assessment of Chemical Mixtures; the other guidelines appear elsewhere in today's Federal Register.

The Guidelines for the Health Risk Assessment of Chemical Mixtures (hereafter "Guidelines") are intended to guide Agency analysis of information relating to health effects data on chemical mixtures in line with the policies and procedures established in the statutes administered by the EPA. These Guidelines were developed as part of an interoffice guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA) in the Agency's Office of Research and Development. They reflect Agency consideration of public and Science Advisory Board (SAB) comments on the Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures published January 9, 1985 (50 FR 1170).

This publication completes the first round of risk assessment guidelines development. These Guidelines will be revised, and new guidelines will be developed, as appropriate.

**EFFECTIVE DATE:** The Guidelines will be effective September 24, 1986.

**FOR FURTHER INFORMATION CONTACT:** Dr. Richard Hertzberg, Waste Management Division, U.S. Environmental Protection Agency, Atlanta Federal Center, 100 Alabama St., SW, Atlanta, GA 30303-3104, TEL: 404-562-8663.

**SUPPLEMENTARY INFORMATION:** In 1983, the National Academy of Sciences (NAS) published its book entitled *Risk Assessment in the Federal Government: Managing the Process.* In that book, the NAS recommended that Federal regulatory agencies establish "inference guidelines" to ensure consistency and technical quality in risk assessments and to ensure that the risk assessment process was maintained as a scientific effort separate from risk management. A task force within EPA accepted that recommendation and requested that Agency scientists begin to develop such guidelines.

**General**

The guidelines published today are products of a two-year Agencywide effort, which has included many scientists from the larger scientific community. These guidelines set forth principles and procedures to guide EPA scientists in the conduct of Agency risk assessments, and to inform Agency decision makers and the public about these procedures. In particular, the guidelines emphasize that risk assessments will be conducted on a case-by-case basis, giving full consideration to all relevant scientific information. This case-by-case approach means that Agency experts review the scientific information on each agent and use the most scientifically appropriate interpretation to assess risk. The guidelines also stress that this information will be fully presented in Agency risk assessment documents, and that Agency scientists will identify the strengths and weaknesses of each assessment by describing uncertainties, assumptions, and limitations, as well as the scientific basis and rationale for each assessment.

Finally, the guidelines are formulated in part to bridge gaps in risk assessment methodology and data. By identifying these gaps and the importance of the missing information to the risk assessment process, EPA wishes to encourage research and analysis that will lead to new risk assessment methods and data.

**Guidelines for Health Risk Assessment of Chemical Mixtures**

Work on the Guidelines for the Health Risk Assessment of Chemical Mixtures began in January 1984. Draft guidelines were developed by Agency work groups composed of expert scientists from throughout the Agency. The drafts were peer-reviewed by expert scientists in the fields of toxicology, pharmacokinetics, and statistics from universities, environmental groups, industry, labor, and other governmental agencies. They were then proposed for public comment in the Federal Register (50 FR 1170). On November 9, 1984, the Administrator directed that Agency offices use the proposed guidelines in performing risk assessments until final guidelines became available.

After the close of the public comment period, Agency staff prepared summaries of the comments, analyses of the major issues presented by the commentators, and preliminary Agency responses to those comments. These analyses were presented to review panels of the SAB on March 4 and April 22-23, 1985, and to the Executive Committee of the SAB on April 25-26, 1985. The SAB meetings were announced in the Federal Register as follows: February 12, 1985 (50 FR 5811), and April 4, 1985 (50 FR 13420 and 13421).

In a letter to the Administrator dated June 19, 1985, the Executive Committee generally concurred on all five of the guidelines, but recommended certain revisions and requested that any revised guidelines be submitted to the appropriate SAB review panel chairman for review and concurrence on behalf of the Executive Committee. As described in the responses to comments (see Part B: Response to the Public and Science Advisory Board Comments), each guidelines document was revised, where appropriate, consistent with the SAB recommendations, and revised draft guidelines were submitted to the panel chairmen. Revised draft Guidelines for the Health Risk Assessment of Chemical Mixtures were concurred on in a letter dated August 16, 1985. Copies of the letters are available at the Public Information Reference Unit, EPA Headquarters Library, as indicated elsewhere in this notice.

Following this Preamble are two parts: Part A contains the Guidelines and Part B the Response to the Public and Science Advisory Board Comments (a summary of the major public comments, SAB comments, and Agency responses to those comments).

The SAB requested that the Agency develop a technical support document for these Guidelines. The SAB identified the need for this type of document due to the limited knowledge on interactions of chemicals in biological systems. Because of this, the SAB commented that progress in improving risk assessment will be particularly dependent upon progress in the science of interactions.

Agency staff have begun preliminary work on the technical support document and expect it to be completed by early 1987. The Agency is continuing to study the risk assessment issues raised in the guidelines and will revise these Guidelines in line with new information as appropriate.

References, supporting documents, and comments received on the proposed guidelines, as well as copies of the final guidelines, are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street, SW, Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

I certify that these Guidelines are not major rules as defined by Executive Order 12291, because they are nonbinding policy statements and have no direct effect on the regulated community.

Therefore, they will have no effect on costs or prices, and they will have no other significant adverse effects on the economy. These Guidelines were reviewed by the Office of Management and Budget under Executive Order 12291.

Dated: August 22, 1986

Signed by EPA Administrator
Lee M. Thomas

# PART A: GUIDELINES FOR THE HEALTH RISK ASSESSMENT OF CHEMICAL MIXTURES

## 1. INTRODUCTION

The primary purpose of this document is to generate a consistent Agency approach for evaluating data on the chronic and subchronic effects of chemical mixtures. It is a procedural guide that emphasizes broad underlying principles of the various science disciplines (toxicology, pharmacology, statistics) necessary for assessing health risk from chemical mixture exposure. Approaches to be used with respect to the analysis and evaluation of the various data are also discussed.

It is not the intent of these Guidelines to regulate any social or economic aspects concerning risk of injury to human health or the environment caused by exposure to a chemical agent(s). All such action is addressed in specific statutes and federal legislation and is independent of these Guidelines.

While some potential environmental hazards involve significant exposure to only a single compound, most instances of environmental contamination involve concurrent or sequential exposures to a mixture of compounds that may induce similar or dissimilar effects over exposure periods ranging from short-term to lifetime. For the purposes of these Guidelines, mixtures will be defined as any combination of two or more chemical substances regardless of source or of spatial or temporal proximity. In some instances, the mixtures are highly complex, consisting of scores of compounds that are generated simultaneously as byproducts from a single source or process (e.g., coke oven emissions and diesel exhaust). In other cases, complex mixtures of related compounds are produced as commercial products (e.g., PCBs, gasoline and pesticide formulations) and eventually released to the environment. Another class of mixtures consists of compounds, often unrelated chemically or commercially, which are placed in the same area for disposal or storage, eventually come into contact with each other, and are released as a mixture to the environment. The quality and quantity of pertinent information available for risk assessment varies considerably for different mixtures. Occasionally, the chemical composition of a mixture is well characterized, levels of exposure to the population are known, and detailed toxicologic data on the mixture are available. Most frequently, not all components of the mixture are known, exposure data are uncertain, and toxicologic data on the known components of the mixture are limited. Nonetheless, the Agency may be required to take action because of the number of individuals at potential risk or because of the known toxicologic effects of these compounds that have been identified in the mixture.

The prediction of how specific mixtures of toxicants will interact must be based on an understanding of the mechanisms of such interactions. Most reviews and texts that discuss toxicant interactions attempt to discuss the biological or chemical bases of the interactions (e.g., Klaassen and Doull, 1980; Levine, 1973; Goldstein et al., 1974; NRC, 1980a; Veldstra, 1956; Withey, 1981). Although different authors use somewhat different classification schemes when discussing the ways in which toxicants interact, it generally is recognized that toxicant interactions may occur during any of the toxicologic processes that take place with a single compound: absorption, distribution, metabolism, excretion, and activity at the receptor site(s). Compounds may interact chemically, yielding a new toxic component or causing a change in the biological availability of the existing component. They may also interact by causing different effects at different receptor sites.

Because of the uncertainties inherent in predicting the magnitude and nature of toxicant interactions, the assessment of health risk from chemical mixtures must include a thorough discussion of all assumptions. No single approach is recommended in these Guidelines. Instead, guidance is given for the use of several approaches depending on the nature and quality of the data. Additional mathematical details are presented in Section 4.

In addition to these Guidelines, a supplemental technical support document is being developed which will contain a thorough review of all available information on the toxicity of chemical mixtures and a discussion of research needs.

## 2. PROPOSED APPROACH

No single approach can be recommended to risk assessments for multiple chemical exposures. Nonetheless, general guidelines can be recommended depending on the type of mixture, the known toxic effects of its components, the availability of toxicity data on the mixture or similar mixtures, the known or anticipated interactions among components of the mixture, and the quality of the exposure data. Given the complexity of this issue and the relative paucity of empirical data from which sound generalizations can be constructed, emphasis must be placed on flexibility, judgment, and a clear articulation of the assumptions and limitations in any risk assessment that is developed. The proposed approach is summarized in Table 1 and Figure 1 and is detailed below. An alphanumeric scheme for ranking the quality of the data used in the risk assessment is given in Table 2.

### 2.1. DATA AVAILABLE ON THE MIXTURE OF CONCERN

For predicting the effects of subchronic or chronic exposure to mixtures, the preferred approach usually will be to use subchronic or chronic health effects data on the mixture of

**Table 1. Risk assessment approach for chemical mixtures**

1. Assess the quality of the data on interactions, health effects, and exposure (see Table 2).
   a. If adequate, proceed to Step 2.
   b. If inadequate, proceed to Step 14.
2. Health effects information is available on the chemical mixture of concern.
   a. If yes, proceed to Step 3.
   b. If no, proceed to Step 4.
3. Conduct risk assessment on the mixture of concern based on health effects data on the mixture. Use the same procedures as those for single compounds. Proceed to Step 7 (optional) and Step 12.
4. Health effects information is available on a mixture that is similar to the mixture of concern.
   a. If yes, proceed to Step 5.
   b. If no, proceed to Step 7.
5. Assess the similarity of the mixture on which health effects data are available to the mixture of concern, with emphasis on any differences in components or proportions of components, as well as the effects that such differences would have on biological activity.
   a. If sufficiently similar, proceed to Step 6.
   b. If not sufficiently similar, proceed to Step 7.
6. Conduct risk assessment on the mixture of concern based on health effects data on the similar mixture. Use the same procedures as those for single compounds. Proceed to Step 7 (optional) and Step 12.
7. Compile health effects and exposure information on the components of the mixture.
8. Derive appropriate indices of acceptable exposure and/or risk on the individual components in the mixture. Proceed to Step 9.
9. Assess data on interactions of components in the mixtures.
   a. If sufficient quantitative data are available on the interactions of two or more components in the mixture, proceed to Step 10.
   b. If sufficient quantitative data are not available, use whatever information is available to qualitatively indicate the nature of potential interactions. Proceed to Step 11.
10. Use an appropriate interaction model to combine risk assessments on compounds for which data are adequate, and use an additivity assumption for the remaining compounds. Proceed to Step 11 (optional) and Step 12.
11. Develop a risk assessment based on an additivity approach for all compounds in the mixture. Proceed to Step 12.
12. Compare risk assessments conducted in Steps 5, 8, and 9. Identify and justify the preferred assessment, and quantify uncertainty, if possible. Proceed to Step 13.
13. Develop an integrated summary of the qualitative and quantitative assessments with special emphasis on uncertainties and assumptions. Classify the overall quality of the risk assessment, as indicated in Table 2. Stop.
14. No risk assessment can be conducted because of inadequate data on interactions, health effects, or exposure. Qualitatively assess the nature of any potential hazard and detail the types of additional data necessary to support a risk assessment. Stop.

Note—Several decisions used here, especially those concerning adequacy of data and similarity between two mixtures, are not precisely characterized and will require considerable judgment. See text.

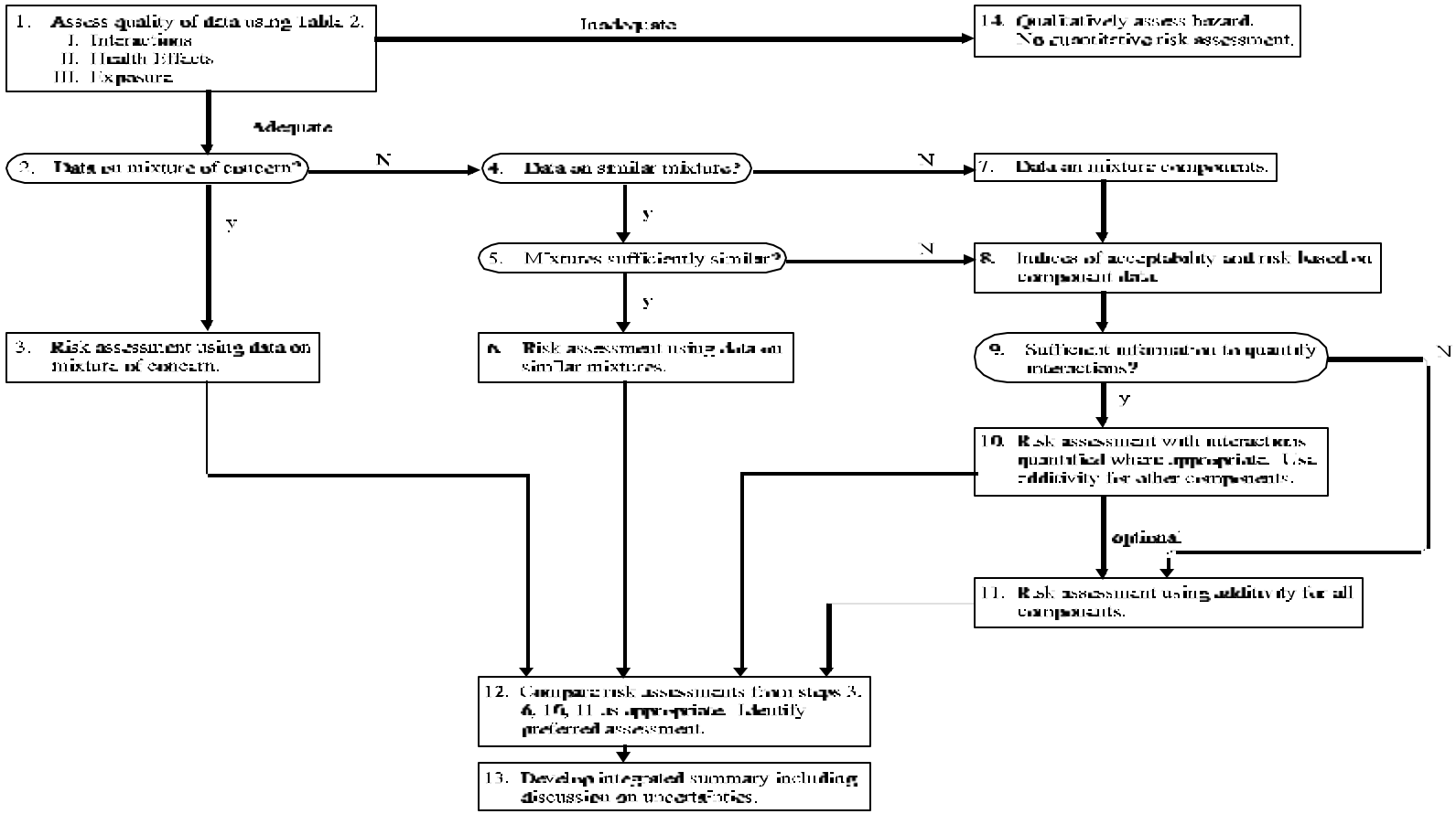


**Figure 1. Flow chart of the risk assessment in Table 1. Note that it may be desirable to conduct all three assessments when possible (i.e., using data on the mixture, a similar mixture, or the components) in order to make the fullest use of the available data. See text for further discussion.**

**Table 2. Classification scheme for the quality of the risk assessment of the mixture[a]**

*Information on Interactions*

I. Assessment is based on data on the mixture of concern.
II. Assessment is based on data on a sufficiently similar mixture.
III. Quantitative interactions of components are well characterized.
IV. The assumption of additivity is justified based on the nature of the health effects and on the number of component compounds.
V. An assumption of additivity cannot be justified, and no quantitative risk assessment can be conducted.

*Health Effects Information*

A. Full health effects data are available and relatively minor extrapolation is required.
B. Full health effects data are available but extensive extrapolation is required for route or duration of exposure or for species differences. These extrapolations are supported by pharmacokinetic considerations, empirical observations, or other relevant information.
C. Full health effects data are available, but extensive extrapolation is required for route or duration of exposure or for species differences. These extrapolations are not directly supported by the information available.
D. Certain important health effects data are lacking and extensive extrapolations are required for route or duration of exposure or for species differences.
E. A lack of health effects information on the mixture and its components in the mixture precludes a quantitative risk assessment.

*Exposure Information[b]*

1. Monitoring information either alone or in combination with modeling information is sufficient to accurately characterize human exposure to the mixture or its components.
2. Modeling information is sufficient to reasonably characterize human exposure to the mixture or its components.
3. Exposure estimates for some components are lacking, uncertain, or variable. Information on health effects or environmental chemistry suggests that this limitation is not likely to substantially affect the risk assessment.
4. Not all components in the mixture have been identified, or levels of exposure are highly uncertain or variable. Information on health effects or environmental chemistry is not sufficient to assess the effect of this limitation on the risk assessment.
5. The available exposure information is insufficient for conducting a risk assessment.

[a]See text for discussion of sufficient similarity, adequacy of data, and justification for additivity assumptions.
[b]See the Agency's Guidelines for Estimating Exposures (U.S. EPA, 1986d) for more complete information on performing exposure assessments and evaluating the quality of exposure data.

concern and adopt procedures similar to those used for single compounds, either systemic toxicants or carcinogens (see U.S. EPA, 1986a-c). The risk assessor must recognize, however, that dose-response models used for single compounds are often based on biological mechanisms of the toxicity of single compounds, and may not be as well justified when applied to the mixture as a whole. Such data are most likely to be available on highly complex mixtures, such as coke oven emissions or diesel exhaust, which are generated in large quantities and associated with or suspected of causing adverse health effects. Attention should also be given to the persistence of the mixture in the environment as well as to the variability of the mixture composition over time or from different sources of emissions. If the components of the mixture are known to partition into different environmental compartments or to degrade or transform at different rates in the environment, then those factors must also be taken into account, or the confidence in and applicability of the risk assessment are diminished.

## 2.2. DATA AVAILABLE ON SIMILAR MIXTURES

If the risk assessment is based on data from a single mixture that is known to be generated with varying compositions depending on time or different emission sources, then the confidence in the applicability of the data to a risk assessment also is diminished. This can be offset to some degree if data are available on several mixtures of the same components that have different component ratios which encompass the temporal or spatial differences in composition of the mixture of concern. If such data are available, an attempt should be made to determine if significant and systematic differences exist among the chemical mixtures. If significant differences are noted, ranges of risk can be estimated based on the toxicologic data of the various mixtures. If no significant differences are noted, then a single risk assessment may be adequate, although the range of ratios of the components in the mixtures to which the risk assessment applies should also be given.

If no data are available on the mixtures of concern, but health effects data are available an a similar mixture (i.e., a mixture having the same components but in slightly different ratios, or having several common components but lacking one or more components, or having one or more additional components), a decision must be made whether the mixture on which health effects data are available is or is not "sufficiently similar" to the mixture of concern to permit a risk assessment. The determination of "sufficient similarity" must be made on a case-by-case basis, considering not only the uncertainties associated with using data on a dissimilar mixture but also the uncertainties of using other approaches such as additivity. In determining reasonable similarity, consideration should be given to any information on the components that differ or are contained in markedly different proportions between the mixture

on which health effects data are available and the mixture of concern. Particular emphasis should be placed on any toxicologic or
pharmacokinetic data on the components or the mixtures which would be useful in assessing the significance of any chemical difference between the similar mixture and the mixtures of concern.

Even if a risk assessment can be made using data on the mixtures of concern or a reasonably similar mixture, it may be desirable to conduct a risk assessment based on toxicity data on the components in the mixture using the procedure outlined in Section 2.B. In the case of a mixture containing carcinogens and toxicants, an approach based on the mixture data alone may not be sufficiently protective in all cases. For example, this approach for a two-component mixture of one carcinogen and one toxicant would use toxicity data on the mixture of the two compounds. However, in a chronic study of such a mixture, the presence of the toxicant could mask the activity of the carcinogen. That is to say, at doses of the mixture sufficient to induce a carcinogenic effect, the toxicant could induce mortality so that at the maximum tolerated dose of the mixture, no carcinogenic effect could be observed. Since carcinogenicity is considered by the Agency to be a nonthreshold effect, it may not be prudent to construe the negative results of such a bioassay as indicating the absence of risk at lower doses. Consequently, the mixture approach should be modified to allow the risk assessor to evaluate the potential for masking, of one effect by another, on a case-by-case basis.

## 2.3. DATA AVAILABLE ONLY ON MIXTURE COMPONENTS

If data are not available on an identical or reasonably similar mixture, the risk assessment may be based on the toxic or carcinogenic properties of the components in the mixture. When little or no quantitative information is available on the potential interaction among the components, additive models (defined in the next section) are recommended for systemic toxicants. Several studies have demonstrated that dose additive models often predict reasonably well the toxicities of mixtures composed of a substantial variety of both similar and dissimilar compounds (Pozzani et al., 1959; Smyth et al., 1969, 1970; Murphy, 1980). The problem of multiple toxicant exposure has been addressed by the American Conference of Governmental Industrial Hygienists (ACGIH, 1983), the Occupational Safety and Health Administration (OSHA, 1983), the World Health Organization (WHO, 1981), and the National Research Council (NRC, 1980a,b). Although the focus and purpose of each group was somewhat different, all groups that recommended an approach elected to adopt some type of dose additive model. Nonetheless, as discussed in Section 4, dose additive models are not the most biologically plausible approach if the compounds do not have the same mode of toxicologic action. Consequently, depending on the nature of the risk assessment and the available information on modes

of action and patterns of joint action, the Federal Register most reasonable additive model should be used.

### 2.3.1. Systemic Toxicants

For systemic toxicants, the current risk assessment methodology used by the Agency for single compounds most often results in the derivation of an exposure level which is not anticipated to cause significant adverse effects. Depending on the route of exposure, media of concern, and the legislative mandate guiding the risk assessments, these exposure levels may be expressed in a variety of ways such as acceptable daily intakes (ADIs) or reference doses (RfDs), levels associated with various margins of safety (MOS), or acceptable concentrations in various media. For the purpose of this discussion, the term "acceptable level" (AL) will be used to indicate any such criteria or advisories derived by the Agency. Levels of exposure (E) will be estimates obtained following the most current Agency Guidelines for Estimating Exposures (U.S. EPA, 1986d). For such estimates, the "hazard index" (HI) of a mixture based on the assumption of dose addition may be defined as:

$$HI = E_1/AL_1 + E_2/AL_2 + \ldots + E_i/AL_i \qquad (2\text{-}1)$$

where:

$E_i$ = exposure level to the $i^{th}$ toxicant* and $AL_i$ = maximum acceptable level for the $i^{th}$ toxicant.

Since the assumption of dose addition is most properly applied to compounds that induce the same effect by similar modes of action, a separate hazard index should be generated for each end point of concern. Dose addition for dissimilar effects does not have strong scientific support, and, if done, should be justified on a case-by-case basis in terms of biological plausibility.

The assumption of dose addition is most clearly justified when the mechanisms of action of the compounds under consideration are known to be the same. Since the mechanisms of action for most compounds are not well understood, the justification of the assumption of dose addition will often be limited to similarities in pharmacokinetic and toxicologic characteristics. In any event, if a hazard index is generated the quality of the experimental evidence supporting the assumption of dose addition must be clearly articulated.

The hazard index provides a rough measure of likely toxicity and requires cautious interpretation. The hazard index is only a numerical indication of the nearness to acceptable limits of

exposure or the degree to which acceptable exposure levels are exceeded. As this index approaches unity, concern for the potential hazard of the mixture increases. If the index exceeds unity, the concern is the same as if an individual chemical exposure exceeded its acceptable level by the same proportion. The hazard index does not define dose-response relationships, and its numerical value should not be construed to be a direct estimate of risk. Nonetheless, if sufficient data are available to derive individual acceptable levels for a spectrum of effects (e.g., MFO induction, minimal effects in several organs, reproductive effects, and behavioral effects), the hazard index may suggest what types of effects might be expected from the mixture exposure. If the components' variabilities of the acceptable levels are known, or if the acceptable levels are given as ranges (e.g., associated with different margins of safety), then the hazard index should be presented with corresponding estimates of variation or range.

Most studies on systemic toxicity report only descriptions of the effects in each dose group. If dose-response curves are estimated for systemic toxicants, however, dose-additive or response-additive assumptions can be used, with preference given to the most biologically plausible assumption (see Section 4 for the mathematical details).

### 2.3.2. Carcinogens

For carcinogens, whenever linearity of the individual dose-response curves has been assumed (usually restricted to low doses), the increase in risk P (also called excess or incremental risk), caused by exposure d, is related to carcinogenic potency B, as:

$$P = d\,B \qquad (2\text{-}2)$$

For multiple compounds, this equation may be generalized to:

$$P = \sum d_i B_i \qquad (2\text{-}3)$$

This equation assumes independence of action by the several carcinogens and is equivalent to the assumption of dose addition as well as to response addition with completely negative correlation of tolerance, as long as $P < 1$ (see Section 4). Analogous to the procedure used in Equation 2-1 for systemic toxicants, an index for n carcinogens can be developed by dividing exposure levels (E) by doses (DR) associated with a set level of risk:

$$HI = E_1/DR_1 + E_2/DR_2 + \ldots + E_n/DR_n \qquad (2\text{-}4)$$

Note that the less linear the dose-response curve is, the less appropriate Equations 2-3 and 2-4 will be, perhaps even at low doses. It should be emphasized that because of the uncertainties in estimating dose-response relationships for single compounds, and the additional uncertainties in combining the individual estimate to assess response from exposure to mixtures, response rates and hazard indices may have merit in comparing risks but should not be regarded as measures of absolute risk.

### 2.3.3. Interactions

None of the above equations incorporates any form of synergistic or antagonistic interaction. Some types of information, however, may be available that suggest that two or more components in the mixture may interact. Such information must be assessed in terms of both its relevance to subchronic or chronic hazard and its suitability for quantitatively altering the risk assessment.

For example, if chronic or subchronic toxicity or carcinogenicity studies have been conducted that permit a quantitative estimation of interaction for two chemicals, then it may be desirable to consider using equations detailed in Section 4, or modifications of these equations, to treat the two compounds as a single toxicant with greater or lesser potency than would be predicted from additivity. Other components of the mixture, on which no such interaction data are available, could then be separately treated in an additive manner. Before such a procedure is adopted, however, a discussion should be presented of the likelihood that other compounds in the mixture may interfere with the interaction of the two toxicants on which quantitative interaction data are available. If the weight of evidence suggests that interference is likely, then a quantitative alteration of the risk assessment may not be justified. In such cases, the risk assessment may only indicate the likely nature of interactions, either synergistic or antagonistic, and not quantify their magnitudes.

Other types of information, such as those relating to mechanisms of toxicant interaction, or quantitative estimates of interaction between two chemicals derived from acute studies, are even less likely to be of use in the quantitative assessment of long-term health risks. Usually it will be appropriate only to discuss these types of information, indicate the relevance of the information to subchronic or chronic exposure, and indicate, if possible, the nature of potential interactions, without attempting to quantify their magnitudes.

When the interactions are expected to have a minor influence on the mixture's toxicity, the assessment should indicate, when possible, the compounds most responsible for the predicted toxicity. This judgment should be based on predicted toxicity of each component, based on exposure and toxic

or carcinogenic potential. This potential alone should not be used as an indicator of the chemicals posing the most hazard.

### 2.3.4. Uncertainties

For each risk assessment, the uncertainties should be clearly discussed and the overall quality of the risk assessment should be characterized. The scheme outlined in Table 2 should be used to express the degree of confidence in the quality of the data on interaction, health effects, and exposure.

a. Health Effects—In some cases, when health effects data are incomplete, it may be possible to argue by analogy or quantitative structure-activity relationships that the compounds on which no health effects data are available are not likely to significantly affect the toxicity of the mixture. If a risk assessment includes such an argument, the limitations of the approach must be clearly articulated. Since a methodology has not been adopted for estimating an acceptable level (e.g., ADI) or carcinogenic potential for single compounds based either on quantitative structure-activity relationships or on the results of short-term screening tests, such methods are not at present recommended as the sole basis of a risk assessment on chemical mixtures.
b. Exposure Uncertainties—The general uncertainties in exposure assessment have been addressed in the Agency's Guidelines for Estimating Exposures (U.S. EPA, 1986d). The risk assessor should discuss these exposure uncertainties in terms of the strength of the evidence used to quantify the exposure. When appropriate, the assessor should also compare monitoring and modeling data and discuss any inconsistencies as a source of uncertainty. For mixtures, these uncertainties may be increased as the number of compounds of concern increases.

   If levels of exposure to certain compounds known to be in the mixture are not available, but information on health effects and environmental persistence and transport suggest that these compounds are not likely to be significant in affecting the toxicity of the mixture, then a risk assessment can be conducted based on the remaining compounds in the mixture, with appropriate caveats. If such an argument cannot be supported, no final risk assessment can be performed until adequate monitoring data are available. As an interim procedure, a risk assessment may be conducted for those components in the mixture for which adequate exposure and health effects data are available. If the interim risk assessment does not suggest a hazard, there is still concern about the risk from such a mixture because not all components in the mixture have been considered.
c. Uncertainties Regarding Composition of the Mixture—In perhaps a worst-case scenario, information may be lacking not only on health effects and levels of exposure, but also on the identity

of some components of the mixture. Analogous to the procedure described in the previous paragraph, an interim risk assessment can be conducted on those components of the mixture for which adequate health effects and exposure information are available. If the risk is considered unacceptable, a conservative approach is to present the quantitative estimates of risk, along with appropriate qualifications regarding the incompleteness of the data. If no hazard is indicated by this partial assessment, the risk assessment should not be quantified until better health effects and monitoring data are available to adequately characterize the mixture exposure and potential hazards.

# 3. ASSUMPTIONS AND LIMITATIONS

## 3.1. INFORMATION ON INTERACTIONS

Most of the data available on toxicant interactions are derived from acute toxicity studies using experimental animals in which mixtures of two compounds were tested, often in only a single combination. Major areas of uncertainty with the use of such data involve the appropriateness of interaction data from an acute toxicity study for quantitatively altering a risk assessment for subchronic or chronic exposure, the appropriateness of interaction data on two component mixtures for quantitatively altering a risk assessment on a mixture of several compounds, and the accuracy of interaction data on experimental animals for quantitatively predicting interactions in humans.

The use of interaction data from acute toxicity studies to assess the potential interactions on chronic exposure is highly questionable unless the mechanisms of the interaction on acute exposure were known to apply to low-dose chronic exposure. Most known biological mechanisms for toxicant interactions, however, involve some form of competition between the chemicals or phenomena involving saturation of a receptor site or metabolic pathway. As the doses of the toxicants are decreased, it is likely that these mechanisms either no longer will exert a significant effect or will be decreased to an extent that cannot be measured or approximated.

The use of information from two-component mixtures to assess the interactions in a mixture containing more than two compounds also is questionable from a mechanistic perspective. For example, if two compounds are known to interact, either synergistically or antagonistically, because of the effects of one compound on the metabolism or excretion of the other, the addition of a third compound which either chemically alters or affects the absorption of one of the first two compounds could substantially alter the degree of the toxicologic interaction. Usually, detailed studies quantifying toxicant interactions are not available on multicomponent mixtures, and the few studies that are available on such mixtures (e.g., Gullino et al., 1956) do not provide sufficient information to assess the effects of

interactive interference. Concerns with the use of interaction data on experimental mammals to assess interactions in humans is based on the increasing appreciation for systematic differences among species in their response to individual chemicals. If systematic differences in toxic sensitivity to single chemicals exist among species, then it seems reasonable to suggest that the magnitude of toxicant interactions among species also may vary in a systematic manner.

Consequently, even if excellent chronic data are available on the magnitude of toxicant interactions in a species of experimental mammal, there is uncertainty that the magnitude of the interaction will be the same in humans. Again, data are not available to properly assess the significance of this uncertainty.

Last, it should be emphasized that none of the models for toxicant interaction can predict the magnitude of toxicant interactions in the absence of extensive data. If sufficient data are available to estimate interaction coefficients as described in Section 4, then the magnitude of the toxicant interactions for various proportions of the same components can be predicted. The availability of an interaction ratio (observed response divided by predicted response) is useful only in assessing the magnitude of the toxicant interaction for the specific proportions of the mixture which was used to generate the interaction ratio.

The basic assumption in the recommended approach is that risk assessments on chemical mixtures are best conducted using toxicologic data on the mixture of concern or a reasonably similar mixture. While such risk assessments do not formally consider toxicologic interactions as part of a mathematical model, it is assumed that responses in experimental mammals or human populations noted after exposure to the chemical mixture can be used to conduct risk assessments on human populations. In bioassays of chemical mixtures using experimental mammals, the same limitations inherent in species-to-species extrapolation for single compounds apply to mixtures. When using health effects data on chemical mixtures from studies on exposed human populations, the limitations of epidemiologic studies in the risk assessment of single compounds also apply to mixtures. Additional limitations may be involved when using health effects data on chemical mixtures if the components in the mixture are not constant or if the components partition in the environment.

### 3.2. ADDITIVITY MODELS

If sufficient data are not available on the effects of the chemical mixture of concern or a reasonably similar mixture, the proposed approach is to assume additivity. Dose additivity is based on the assumption that the components in the mixture have the same mode of action and elicit the same effects. This assumption will not hold true in most cases, at least for mixtures of systemic toxicants. For

systemic toxicants, however, most single compound risk assessments will result in the derivation of acceptable levels, which, as currently defined, cannot be adapted to the different forms of response additivity as described in Section 4.

Additivity models can be modified to incorporate quantitative data on toxicant interactions from subchronic or chronic studies using the models given in Section 4 or modifications of these models. If this approach is taken, however, it will be under the assumption that other components in the mixture do not interfere with the measured interaction. In practice, such subchronic or chronic interactions data seldom will be available. Consequently, most risk assessments (on mixtures) will be based on an assumption of additivity, as long as the components elicit similar effects.

Dose-additive and response-additive assumptions can lead to substantial errors in risk estimates if synergistic or antagonistic interactions occur. Although dose additivity has been shown to predict the acute toxicities of many mixtures of similar and dissimilar compounds (e.g., Pozzani et al., 1959; Smyth et al., 1969, 1970; Murphy, 1980), some marked exceptions have been noted. For example, Smyth et al. (1970) tested the interaction of 53 pairs of industrial chemicals based on acute lethality in rats. For most pairs of compounds, the ratio of the predicted $LD_{50}$ to observed $LD_{50}$ did not vary by more than a factor of 2. The greatest variation was seen with an equivolume mixture of morpholine and toluene, in which the observed $LD_{50}$ was about five times less than the $LD_{50}$ predicted by dose addition. In a study by Hammond et al. (1979), the relative risk of lung cancer attributable to smoking was 11, while the relative risk associated with asbestos exposure was 5. The relative risk of lung cancer from both smoking and asbestos exposure was 53, indicating a substantial synergistic effect. Consequently, in some cases, additivity assumptions may substantially underestimate risk. In other cases, risk may be overestimated. While this is certainly an unsatisfactory situation, the available data on mixtures are insufficient for estimating the magnitude of these errors. Based on current information, additivity assumptions are expected to yield generally neutral risk estimates (i.e., neither conservative nor lenient) and are plausible for component compounds that induce similar types of effects at the same sites of action.

## 4. MATHEMATICAL MODELS AND THE MEASUREMENT OF JOINT ACTION

The simplest mathematical models for joint action assume no interaction in any mathematical sense. They describe either dose addition or response addition and are motivated by data on acute lethal effects of mixtures of two compounds.

### 4.1. DOSE ADDITION

Dose addition assumes that the toxicants in a mixture behave as if they were dilutions or concentrations of each other, thus the true slopes of the dose-response curves for the individual compounds are identical, and the response elicited by the mixture can be predicted by summing the individual doses after adjusting for differences in potency; this is defined as the ratio of equitoxic doses. Probit transformation typically makes this ratio constant at all doses when parallel straight lines are obtained. Although this assumption can be applied to any model (e.g., the one-hit model in NRC, 1980b), it has been most often used in toxicology with the log-dose probit response model, which will be used to illustrate the assumption of dose addition. Suppose that two toxicants show the following log-dose probit response equations:

$$Y_1 = 0.3 + 3 \log Z_1 \qquad (4\text{-}1)$$

$$Y_2 = 1.2 + 3 \log Z_2 \qquad (4\text{-}2)$$

where $Y_1$ is the probit response associated with a dose of $Z_1$ (i = 1, 2). The potency, p, of toxicant #2 with respect to toxicant #1 is defined by the quantity $Z_1/Z_2$ when $Y_1 = Y_2$ (that is what is meant by equitoxic doses). In this example, the potency, p, is approximately 2. Dose addition assumes that the response, Y, to any mixture of these two toxicants can be predicted by

$$Y = 0.3 + 3 \log (Z_1 + pZ_2) \qquad (4\text{-}3)$$

Thus, since p is defined as $Z_1/Z_2$, Equation 4-3 essentially converts $Z_2$ into an equivalent dose of $Z_1$ by adjusting for the difference in potency. A more generalized form of this equation for any number of toxicants is:

$$Y = a_1 + b \log (f_1 + 3\ f_i p_i) + b \log Z \qquad (4\text{-}4)$$

where:

$a_1$ = the y-intercept of the dose-response equation for toxicant #1
b = the slope of the dose-response lines for the toxicants
$f_i$ = the proportion of the $i^{th}$ toxicant in the mixture
$p_i$ = the potency of the $i^{th}$ toxicant with respect to toxicant #1 (i.e., $Z_1/Z_i$); and
Z = the sum of the individual doses in the mixture.

A more detailed discussion of the derivation of the equations for dose addition is presented by Finney (1971).

## 4.2. RESPONSE ADDITION

The other form of additivity is referred to as response addition. As detailed by Bliss (1939), this type of joint action assumes that the two toxicants act on different receptor systems and that the correlation of individual tolerances may range from completely negative (r = –1) to completely positive (r = + 1). Response addition assumes that the response to a given concentration of a mixture of toxicants is completely determined by the responses to the components and the pairwise correlation coefficient. Taking P as the proportion of organisms responding to a mixture of two toxicants which evoke individual responses of $P_1$ and $P_2$, then.

$$P = P_1 \text{ if } r = 1 \text{ and } P_1 \geq P_2 \qquad (4\text{-}5)$$
$$P = P_2 \text{ if } r = 1 \text{ and } P_1 < P_2 \qquad (4\text{-}6)$$
$$P = P_1 + P_2 (1 - P_1) \text{ if } r = 0 \qquad (4\text{-}7)$$
$$P = P_1 + P_2 \text{ if } r = -1 \text{ and } P \leq 1. \qquad (4\text{-}8)$$

More generalized mathematical models for this form of joint action have been given by Plackett and Hewlett (1948).

## 4.3. INTERACTIONS

All of the above models assume no interactions and therefore do not incorporate measurements of synergistic or antagonistic effects. For measuring toxicant interactions for mixtures of two compounds, Finney (1942) proposed the following modification of Equation 4-4 for dose addition:

$$Y = a_1 + b \log (f_1 + pf_2 + K [pf_1f_2]^{0.5}) + b \log Z \qquad (4\text{-}9)$$

where $a_1$, b, $f_1$, $f_2$, p, and Z are defined as before, and K is the coefficient of interaction. A positive value of K indicates synergism, a negative value indicates antagonism, and a value of zero corresponds to dose addition as in Equation 4-4. Like other proposed modifications of dose addition (Hewlett, 1969), the equation assumes a consistent interaction throughout the entire range of proportions of individual components. To account for such asymmetric patterns of interaction as those observed by Alstott et al. (1973), Durkin (1981) proposed the following modification to Equation 4-9:

$$Y = a_1 + b \log (f_1 + pf_2 + K_1f_1 [pf_1f_2]^{0.5} + K_2f_2[pf_1f_2]^{0.5}) + b \log z \qquad (4\text{-}10)$$

in which $K(pf_1f_2)^{0.5}$ is divided into two components, $K_1f_1 (pf_1f_2)^{0.5}$ and $K_2f_2[pf_1f_2]^{0.5}$. Since $K_1$ and $K_2$ need not have the same sign, apparent instances of antagonism at one receptor site and synergism at another receptor site can be estimated. When $K_1$ and $K_2$ are equal, Equation 4-10 reduces to Equation 4-9.

It should be noted that to obtain a reasonable number of degrees of freedom in the estimation of K in Equation 4-9 or $K_1$ and $K_2$ in Equation 4-10, the toxicity of several different combinations of the two components must be assayed along with assays of the toxicity of the individual components. Since this requires experiments with large numbers of animals, such analyses have been restricted for the most part to data from acute bioassays using insects (e.g., Finney, 1971) or aquatic organisms (Durkin, 1979). Also, because of the complexity of experimental design and the need for large numbers of animals, neither Equation 4-9 nor Equation 4-10 has been generalized or applied to mixtures of more than two toxicants. Modifications of response-additive models to include interactive terms have also been proposed, along with appropriate statistical tests for the assumption of additivity (Korn and Liu, 1983; Wahrendorf et al., 1981).

In the epidemiologic literature, measurements of the extent of toxicant interactions, S, can be expressed as the ratio of observed relative risk to relative risk predicted by some form of additivity assumption. Analogous to the ratio of interaction in classical toxicology studies, $S = 1$ indicates no interaction, $S > 1$ indicates synergism, and $S < 1$ indicates antagonism. Several models for both additive and multiplicative risks have been proposed (e.g., Hogan et al., 1978; NRC, 1980b; Walter, 1976). For instance, Rothman (1976) has discussed the use of the following measurement of toxicant interaction based on the assumption of risk additivity:

$$S = (R_{11} - 1)/(R_{10} + R_{01} - 2) \qquad (4\text{-}11)$$

where $R_{10}$ is the relative risk from compound #1 in the absence of compound #2, $R_{01}$ is the relative risk from compound #2 in the absence of compound #1, and $R_{11}$ is the relative risk from exposure to both compounds. A multiplicative risk model adapted from Walter and Holford (1978, Equation 4) can be stated as:

$$S = R_{11}/(R_{10}\, R_{01}) \qquad (4\text{-}12)$$

As discussed by both Walter and Holford (1978) and Rothman (1976), the risk-additive model is generally applied to agents causing diseases while the multiplicative model is more appropriate to agents that prevent disease. The relative merits of these and other indices have been the subject of considerable discussion in the epidemiologic literature (Hogan et al., 1978; Kupper and Hogan, 1978; Rothman, 1978; Rothman et al., 1980; Walter and Holford, 1978). There seems to be a consensus that for public health concerns regarding causative (toxic) agents, the additive model is more appropriate.

Both the additive and multiplicative models assume statistical independence in that the risk associated with exposure to both compounds in combination can be predicted by the risks associated with separate exposure to the individual compounds. As illustrated by Siemiatycki and Thomas (1981) for multistage carcinogenesis, the better fitting statistical model will depend not only upon actual biological interactions, but also upon the stages of the disease process which the compounds affect. Consequently, there is no a priori basis for selecting either type of model in a risk assessment. As discussed by Stara et al. (1983), the concepts of multistage carcinogenesis and the effects of promoters and cocarcinogens on risk are extremely complex issues. Although risk models for promoters have been proposed (e.g., Bums et al., 1983), no single approach can be recommended at this time.

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## PART B: RESPONSE TO PUBLIC AND SCIENCE ADVISORY BOARD COMMENTS

## 1. INTRODUCTION

This section summarizes some of the major issues raised in public comments on the Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures published on January 9, 1985 (50 FR 1170). Comments were received from 14 individuals or organizations. An issue paper reflecting public and external review comments was presented to the Chemical Mixtures Guidelines Panel of the Science Advisory Board (SAB) on March 4, 1985. At its April 22-23, 1985, meeting, the SAB Panel provided the Agency with additional suggestions and recommendations concerning the Guidelines. This section also summarizes the issues raised by the SAB.

The SAB and public commentators expressed diverse opinions and addressed issues from a variety of perspectives. In response to comments, the Agency has modified or clarified many sections of the Guidelines, and is planning to develop a technical support document in line with the SAB recommendations. The discussion that follows highlights significant issues raised in the comments, and the Agency's response to them. Also, many minor recommendations, which do not warrant discussion here, were adopted by the Agency.

## 2. RECOMMENDED PROCEDURES

### 2.1. DEFINITIONS

Several comments were received concerning the lack of definitions for certain key items and the general understandability of certain sections. Definitions have been rewritten for several terms and the text has been significantly rewritten to clarify the Agency's intent and meaning.

Several commentators noted the lack of a precise definition of "mixture," even though several classes of mixtures are discussed. In the field of chemistry, the term "mixture" is usually differentiated from true solutions, with the former defined as nonhomogeneous multicomponent systems. For these Guidelines, the term "mixture" is defined as ". . any combination of two or more chemicals regardless of spatial or temporal homogeneity of source" (Section 1). These Guidelines are intended to cover risk assessments for any situation where the population is exposed or potentially exposed to two or more compounds of concern. Consequently, the introduction has been revised to clarify the intended breadth of application.

Several commentators expressed concern that "sufficient similarity" was difficult to define and that the Guidelines should give more details concerning similar mixtures. The Agency agrees and is planning research projects to improve on the definition. Characteristics such as composition and toxic end-effects are certainly important, but the best indicators of similarity in terms of risk assessment have yet to be determined. The discussion in the Guidelines emphasizes case-by-case judgment until the necessary research can be performed. The Agency considered but rejected adding an example, because it is not likely that any single example would be adequate to illustrate the variety in the data and types of judgments that will be required in applying this concept. Inclusion of examples is being considered for the technical support document.

## 2.2. MIXTURES OF CARCINOGENS AND SYSTEMIC TOXICANTS

The applicability of the preferred approach for a mixture of carcinogens and systemic (noncarcinogenic) toxicants was a concern of several public commentators as well as the SAB. The Agency realizes that the preferred approach of using test data on the mixture itself may not be sufficiently protective in all cases. For example, take a simple two-component mixture of one carcinogen and one toxicant. The preferred approach would lead to using toxicity data on the mixture of the two compounds. However, it is possible to set the proportions of each component so that in a chronic bioassay of such a mixture, the presence of the toxicant could mask the activity of the carcinogen. That is to say, at doses of the mixture sufficient for the carcinogen to induce tumors in the small experimental group, the toxicant could induce mortality. At a lower dose in the same study, no adverse effects would be observed, including no carcinogenic effects. The data would then suggest use of a threshold approach. Since carcinogenicity is considered by the Agency to be a nonthreshold effect, it may not be prudent to construe the negative results of such a bioassay as indicating the absence of risk at lower doses. Consequently, the Agency has revised the discussion of the preferred approach to allow the risk assessor to evaluate the potential for masking of carcinogenicity or other effects on a case-by-case basis.

Another difficulty occurs with such a mixture when the risk assessment needs to be based on data for the mixture components. Carcinogens and systemic toxicants are evaluated by the Agency using different approaches and generally are described by different types of data: response rates for carcinogens vs. effect descriptions for toxicants. The Agency recognizes this difficulty and recommends research to develop a new assessment model for combining these dissimilar data sets into one risk estimate. One suggestion in the interim is to present separate risk estimates for the dissimilar end points, including carcinogenic, teratogenic, mutagenic, and systemic toxicant components.

# 3. ADDITIVITY ASSUMPTION

Numerous comments were received concerning the assumption of additivity, including:

a. the applicability of additivity to "complex" mixtures;
b. the use of dose additivity for compounds that induce different effects;
c. the interpretation of the Hazard Index; and
d. the use of interaction data.

Parts of the discussion in the proposed guidelines concerning the use of additivity assumptions were vague and have been revised in the final Guidelines to clarify the Agency's intent and position.

## 3.1. COMPLEX MIXTURES

The issue of the applicability of an assumption of additivity to complex mixtures containing tens or hundreds of components was raised in several of the public comments. The Agency and its reviewers agree that as the number of compounds in the mixture increases, an assumption of additivity will become less reliable in estimating risk. This is based on the fact that each component estimate of risk or an acceptable level is associated with some error and uncertainty. With current knowledge, the uncertainty will increase as the number of components increases. In any event, little experimental data are available to determine the general change in the error as the mixture contains more components. The Agency has decided that a limit to the number of components should not be set in these Guidelines. However, the Guidelines do explicitly state that as the number of compounds in the mixture increases, the uncertainty associated with the risk assessment is also likely to increase.

## 3.2. DOSE ADDITIVITY

Commentators were concerned about what appeared to be a recommendation of the use of dose additivity for compounds that induce different effects. The discussion following the dose additivity equation was clarified to indicate that the act of combining all compounds, even if they induce dissimilar effects, is a screening procedure and not the preferred procedure in developing a hazard index. The Guidelines were further clarified to state that dose (or response) additivity is theoretically sound, and therefore best applied for assessing mixtures of similar acting components that do not interact.

### 3.3. INTERPRETATION OF THE HAZARD INDEX

Several comments addressed the potential for misinterpretation of the hazard index, and some questioned its validity, suggesting that it mixes science and value judgments by using "acceptable" levels in the calculation. The Agency agrees with the possible confusion regarding its use and has revised the Guidelines for clarification. The hazard index is an easily derived restatement of dose additivity, and is, therefore, most accurate when used with mixture components that have similar toxic action. When used with components of unknown or dissimilar action, the hazard index is less accurate and should be interpreted only as a rough indication of concern. As with dose addition, the uncertainty associated with the hazard index increases as the number of components increases, so that it is less appropriate for evaluating the toxicity of complex mixtures.

### 3.4. USE OF INTERACTION DATA

A few commentators suggested that any interaction data should be used to quantitatively alter the risk assessment. The Agency disagrees. The current information on interactions is meager, with only a few studies comparing response to the mixture with that predicted by studies on components. Additional uncertainties include exposure variations due to changes in composition, mixture dose, and species differences in the extent of the interaction. The Agency is constructing an interaction data base in an attempt to answer some of these issues. Other comments concerned the use of different types of interaction data. The Guidelines restrict the use of interaction data to that obtained from whole animal bioassays of a duration appropriate to the risk assessment. Since such data are frequently lacking, at least for chronic or subchronic effects, the issue is whether to allow for the use of other information such as acute data, *in vitro* data, or structure-activity relationships to quantitatively alter the risk assessment, perhaps by use of a safety factor. The Agency believes that sufficient scientific upport does not exist for the use of such data in any but a qualitative discussion of possible synergistic or antagonistic effects.

## 4. UNCERTAINTIES AND THE SUFFICIENCY OF THE DATA BASE

In the last two paragraphs of Section II of the Guidelines, situations are discussed in which the risk assessor is presented with incomplete toxicity, monitoring, or exposure data. The SAB, as well as several public commentors, recommended that the "risk management" tone of this section be modified and that the option of the risk assessor to decline to conduct a risk assessment be made more explicit.

This is a difficult issue that must consider not only the quality of the available data for risk assessment, but also the needs of the Agency in risk management. Given the types of poor data often

available, the risk assessor may indicate that the risk assessment is based on limited information and thus contains no quantification of risk. Nonetheless, in any risk assessment, substantial uncertainties exist. It is the obligation of the risk assessor to provide an assessment, but also to ensure that all the assumptions and uncertainties are articulated clearly and quantified whenever possible.

The SAB articulated several other recommendations related to uncertainties, all of which have been followed in the revision of the Guidelines. One recommendation was that the summary procedure table also be presented as a flow chart so that all options are clearly displayed. The SAB further recommended the development of a system to express the level of confidence in the various steps of the risk assessment.

The Agency has revised the summary table to present four major options: risk assessment using data on the mixture itself, data on a similar mixture, data on the mixture's components, or declining to quantify the risk when the data are inadequate. A flow chart of this table has also been added to more clearly depict the various options and to suggest the combining of the several options to indicate the variability and uncertainties in the risk assessment.

To determine the adequacy of the data, the SAB also recommended the development of a system to express the level of confidence associated with various steps in the risk assessment process. The Agency has developed a rating scheme to describe data quality in three areas: interaction, health effects, and exposure. This classification provides a range of five levels of data quality for each of the three areas. Choosing the last level in any area results in declining to perform a quantitative risk assessment due to inadequate data. These last levels are described as follows:

Interactions: An assumption of additivity cannot be justified, and no quantitative risk assessment can be conducted.

Health effects: A lack of health effects information on the mixture and its components precludes a quantitative risk assessment.

Exposure: The available exposure information is insufficient for conducting a risk assessment.

Several commentors, including the SAB, emphasized the importance of not losing these classifications and uncertainties farther along in the risk management process. The discussion of uncertainties has been expanded in the final Guidelines and includes the recommendation that a

discussion of uncertainties and assumptions be included at every step of the regulatory process that uses risk assessment.

Another SAB comment was that the Guidelines should include additional procedures for mixtures with more than one end point or effect. The Agency agrees that these are concerns and revised the Guidelines to emphasize these as additional uncertainties worthy of further research.

## 5. NEED FOR A TECHNICAL SUPPORT DOCUMENT

The third major SAB comment concerned the necessity for a separate technical support document for these Guidelines. The SAB pointed out that the scientific and technical background from which these Guidelines must draw their validity is so broad and varied that it cannot reasonably be synthesized within the framework of a brief set of guidelines. The Agency is developing a technical support document that will summarize the available information on health effects from chemical mixtures, and on interaction mechanisms, as well as identify and develop mathematical models and statistical techniques to support these Guidelines. This document will also identify critical gaps and research needs.

Several comments addressed the need for examples on the use of the Guidelines. The Agency has decided to include examples in the technical support document.

Another issue raised by the SAB concerned the identification of research needs. Because little emphasis has been placed on the toxicology of mixtures until recently, the information on mixtures is limited. The SAB pointed out that identifying research needs is critical to the risk assessment process, and the EPA should ensure that these needs are considered in the research planning process. The Agency will include a section in the technical support document that identifies research needs regarding both methodology and data.