External Peer Review Workshop for "Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects"

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Note

This report was prepared by Eastern Research Group, Inc. (ERG), under contract to the U.S. Environmental Protection Agency (EPA) (Contract No. 68-C-02-060, Task Order 74). The report provides a general record of discussions at the peer review meeting, including reviewer conclusions and recommendations. It does not contain a verbatim transcript of all issues discussed during the peer review meeting, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. Except as specifically noted, no statements in this report represent analyses by or positions of EPA or ERG.

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List of Abbreviations

BMD	benchmark dose
CRA	cumulative risk assessment
CHI	cumulative hazard index
DBP	disinfectant byproduct
EPA	U.S. Environmental Protection Agency
FQPA	Food Quality Protection Act
HI	hazard index
IRIS	Integrated Risk Information System
MOE	margin of exposure
NCEA	National Center for Environmental Assessment
PBDE	polybrominated diphenyl ether
PBPK	physiologically based pharmacokinetic
PCB	polychlorinated biphenyl
RfD	reference dose
RPF	relative potency factors
QSAR	quantitative structure-activity relationship
SAR	structure-activity relationship
TTD	target organ toxicity dose
UF	uncertainty factor

Executive Summary

ERG, under contract to the U.S. Environmental Protection Agency (EPA), organized and implemented a peer review of EPA's external review draft document *Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects* (referred to as the "Approaches Document"). Five experts conducted an independent peer review of the document in a meeting open to the public on May 25–26, 2006, in Cincinnati, Ohio. This report summarizes the results of the peer review.

General Impressions and Overarching Issues

The peer reviewers commented that EPA's Approaches Document focuses on approaches and tools that facilitate the consideration of "integrative multiples" in the context of cumulative risk assessment (CRA). They thought that the document is well-written, timely, and represents forward thinking in the complex area of CRA. It is not a regulatory guidance document and does not describe any methods and tools that are entirely new or novel. However, it does build on the current concepts and tools that relate to the consideration of issues relating to the integrative multiples. The main contribution of the Approaches Document is putting all ideas in one place, so users can consider all possible options.

The panel appreciated the population focus of this document even though there is concern about the feasibility of applying the approaches and tools to large risk assessments and complex scenarios. A particularly original aspect of this document is the manner in which the iteration and cooperation between the exposure assessment and toxicity assessment phases are emphasized and presented. However, the panel felt that the role and place of the various approaches should be clearly identified within the larger picture of CRA for source-based and health effects-based assessments.

The panel suggested the following overarching recommendations:

- Drop the term "alternative" from the title of the document.
- Include biomonitoring data at all levels of the CRA process.
- Include a continuous example throughout the document.
- Consider presenting the CRA approaches outlined in the document at a workshop at the Society for Risk Analysis (SRA).
- Make the full Approaches Document available on EPA's Web site and consider publishing reports in peer-reviewed journals (e.g., *Risk Analysis, Environmental Health Perspectives, American Journal of Public Health,* and *Regulatory Toxicology and Pharmacology*) to reach the wider scientific communities.

Key Comments on Chapter 1

The panel thought that the level of detail in Chapter 1 was adequate. However, they noted that different triggers of CRAs will require different types of investigation. They were specifically concerned about the approach when health endpoints are the trigger. Some panelists were also concerned that the document makes too sharp a distinction between threshold and non-threshold

effects. They suggested that the benchmark dose (BMD) approach might allow for alternatives to the hazard index (HI) and margin of exposure (MOE) approaches. The panel recommended the following:

- Apply response additivity only to carcinogens that act by a non-threshold mechanism.
- Incorporate clearer definitions of response additivity and dose additivity.

Key Comments on Chapter 2

The panel commented that Chapter 2 contains appropriate detail in describing EPA's approach for assessing multiple chemicals, exposures, and effects. It adequately sets the stage for discussions in Chapters 3 and 4, however, is less successful for Chapter 5 since the structures are not parallel. The panel felt there was a lack of a comprehensive inventory of factors that contribute to risks and to the perception of risks in a community. They suggested that communities can bring valuable information about elevated diseases to the risk assessment process. The panel recommended the following:

- Add reference to the Agency for Toxic Substances and Disease Registry's (ATSDR's) Toxicological Profiles for Chemical Mixtures.
- Acknowledge the efforts of other national and international agencies that address cumulative risks.
- Clearly state that health risks from exposure should be determined based on the most vulnerable population. However, if a CRA is triggered by a subpopulation, it is important that the whole population continue to be the focus of the assessment, because exposure is rarely limited to a subgroup.
- Include an elevation in rates of an unexpected disease in the population, as well as the community's perception of elevated disease as criteria for chemical selection.
- Consider exposure of a large population to chemicals of lower toxicity.
- Delay limiting the scope of the risk assessment (i.e., through screening) as long as possible to avoid inadvertently eliminating important chemicals and routes of exposure.
- Discuss potential interactions between traditional EPA concerns (e.g., chemicals from waste sites) with typical household exposures to chemicals in items such as cleaning products.
- Even though the focus of this document is on chemical exposures, do not ignore contributing socio-economic factors in the CRA.
- Include a version of Figure 5-2 in Chapter 2.
- Add the figure drafted by the panel to Chapter 2 (see Section 4.3).

Key Comments on Chapter 3

The panel agreed that Chapter 3 was of good scientific quality and a useful compendium of currently practiced exposure assessment methods, but could use some improvement. The chapter emphasizes modeling almost to the exclusion of measurement or monitoring. Most exposure assessors believe that measurements are preferable to modeling, and modeling should not

preclude other approaches. The panel also commented that undertaking a large multiple chemical, multiple pathway, multiple receptor risk assessment using the methods described in Chapter 3 would be extremely resource-intensive. The grouping concept is a new technique; however, the panel was unclear how the concept will facilitate exposure assessment since most chemicals behave differently from one another. They also thought that the calendar approach would be difficult to implement in a large assessment. The panel recommended the following:

- Add a figure identifying the hierarchy of exposure assessment.
- Define the goals of the exposure assessment. The selection and characterization of receptors may depend on the goal of the exposure assessment.
- Discuss data quality and feasibility to support various levels of models.
- Include a discussion of retrospective dose reconstruction when health outcomes are observed.
- Include citations to works that integrate site-specific information into chemical degradation evaluations.
- Consider the amount of resources to be expended on the assessment and whether the goals of the assessment warrant the use of these resources.
- Integrate the use of probabilistic risk assessment.
- Include stronger statements that children are more vulnerable.
- Add a discussion of chemical-chemical interaction in the environment and how it can be assessed in a CRA.
- Emphasize dermal exposures more.

Key Comments on Chapter 4

The panel concluded that the tools and concepts relating to multi-route exposures, evaluation of secondary and tertiary effects, as well as toxicological interactions are spelled out nicely and clearly in Chapter 4. However, they were concerned that the idea of changing dose-response analysis so that it occurs concurrently and iteratively with exposure assessment will have major implications. The panel also expressed concern over the complexities of congeners and metabolites acting differently. The panel recommended the following:

- Provide a better description of the categorical regression approach as a method of analysis in CRA.
- Specify ways and means of using internal dose in computing HI.
- Clarify how the interaction magnitude for modifying the HI is computed.
- Discuss the use of the current knowledge on genetic epidemiology in the context of CRA.
- Add a figure in Section 4.4.1 to present the various levels of information and confidence associated with them.
- Include additional discussion on time-related dose-response and existing methodologies. A possible alternative to concurrent dose-response analysis is to employ “look-up” criteria for more time points such as acute, subacute, and subchronic.

- Consider indirect actions of chemicals and mixtures.
- Acknowledge the toxicological data gap for certain chemicals and address how it will be handled in the CRA. Add language regarding the confidence/uncertainty of the data on secondary effects, since they may not come directly from an authoritative database.
- Discuss whether the target organ toxicity dose (TTD) concept can be used for cancer endpoints.
- Develop a method to add doses of chemicals with unequal dose-response metrics.
- Discuss the level of aggregation and resulting uncertainty when using grouping methods.

Key Comments on Chapter 5

The panel thought that Chapter 5 adequately acknowledged the uncertainties associated with CRA. However, they commented that Section 5.4 could be expanded to further delineate the sources of uncertainties (using a variety of tools) introduced by certain methods. Risk communication is a major concern and undertaking when CRA is involved. There is particular concern about the interface between values calculated and incidence of disease in a real population. The cumulative hazard index (CHI) approach is challenging when trying to apply these results to explain health issues in a community. The panel did not think that Chapter 5 adequately addressed risk characterization when health effects are the trigger for a CRA. In these cases, the analytic methods need to be in context of a multi-factorial risk perspective, and a traditional epidemiologic investigation may be required. There needs to be some way of associating the risk characterization results to the endpoints that are the triggers for the assessment. The panel also discussed harmonizing risk characterization of cancer and non-cancer effects and suggested that the BMD approach offers an opportunity to estimate the probability of non-cancer effects. The panel recommended the following:

- Clearly summarize the trigger issues and scope of the CRA as they relate to Chapters 1 and 2.
- Consider integrating concepts from classical causation or evidence-based toxicology to make risk assessment results more realistic.
- Discuss the hierarchy of screening (grouping) approaches, sophisticated stochastic models to account for multiples, and the data requirements.
- Add a crude approach of grouping based on structure-activity relationship (SAR) as an option to be used in conjunction with the exposure grouping in the initial ranking of chemicals.
- Discuss how the results of the CRA can be used, and provide a summary of the types of CRA that would be more appropriate for certain triggers and purposes.
- Further examine and discuss the impact of uncertainty factors when reference doses (RfDs) are used.
- Include a section to discuss limitations and interpretation of existing methods to characterize cumulative risk when health outcome is a trigger. While all risk characterization approaches described in the Approaches Document have utility, they are not of value for all situations.
- Include a more detailed discussion on the interpretation of the outcomes of probabilistic and ordinal regression analyses.

- Describe and consider options to expand the results of a CRA to rank public health impacts for risk management evaluation.
- Clarify that only a couple of approaches are considered as examples or add a discussion in context of risk characterization, limitation, and interpretation about the other available methods.
- Describe the factors that determine the level of “acceptability” of extrapolation, simplifications, and omissions.
- Explain the relationship between Section 5.3.3 and the method of estimating joint toxicity described in Chapter 4.
- Add a discussion on data quality and their appropriateness for the various CRA options.
- Modify Figure 5-1 or include additional discussion in the text.

1.0 Introduction

This report summarizes an independent peer review, by five experts, of the U.S. Environmental Protection Agency's (EPA's) external review draft document *Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects* (EPA 2006). The document was prepared by EPA's National Center for Environmental Assessment (NCEA) in Cincinnati. This report refers to the review document as the "Approaches Document." The peer review took place at a meeting on May 25–26, 2006, in Cincinnati, Ohio. The meeting was open to the public as observers, either in person or by telephone. ERG, under contract to EPA, organized and facilitated the entire peer review. This introductory section provides background information on the review document (Section 1.1), describes the scope of the peer review (Section 1.2), and outlines the organization of this report (Section 1.3).

1.1 Background

Public interest in the environment continues to grow as more information is shared about multiple chemicals in air, water, and soil from different sources, with health risks being a major concern. EPA has responded to increasing requests for a way to understand and evaluate the combined impacts of these conditions by preparing a set of overarching reports on cumulative risk assessment (CRA). Those documents have provided information to help explain, scope, and organize CRAs. A recent report defined the general framework for these assessments (EPA 2003), and earlier reports laid the broad foundation for up-front thinking (EPA 1997, 2002). Additional documents have been prepared to address focused cumulative risk issues within specific programs, and further efforts are under way.

The review document is the next in a series of Agency reports on cumulative risk, and it represents an initial step toward guidelines for implementing these assessments. Building on the concepts that have been identified in earlier reports and offering examples to illustrate how those concepts can be applied, this initial guidance focuses on health risks associated with multiple sources, chemicals, and exposures at contaminated sites. With stressors limited to chemicals and effects limited to human health, the document's scope is much narrower than that of a comprehensive assessment that would cover all aspects of cumulative risk.

The purpose of this guidance is to offer information that can be used to implement basic cumulative risk concepts within the framework set forth by EPA, focusing on one type of application. By addressing many different pieces of the risk picture together (from sources to effects), this guidance is designed to support an assessment of "integrated multiples" for human health at contaminated sites.

Many approaches described in the draft report can, however, also be applied to assess similar risk issues beyond a site application. As with any general guidance, the document is only advisory. The EPA Program and Regional Offices have the responsibility to implement these concepts in their program-specific risk guidance.

1.2 Scope of the Peer Review

ERG managed every aspect of the peer review, including selecting reviewers and coordinating activities before, during, and after the peer review meeting.

1.2.1 Selecting the Peer Reviewers

ERG selected peer reviewers that met the selection criteria specified by EPA in its task order for this project. Those criteria noted that: "Participants shall have expertise, experience and qualifications from one or more of the following expert categories:

- exposure assessment (could include modeling and measurement)
- experimental toxicology of systemic effects
- mixtures risk assessment methodology (including dose response of joint toxicity)
- statistical modeling and uncertainty analysis
- risk analysis involving stakeholder participation or environmental justice issues."

Based on these selection criteria, ERG conducted a search of subject matter experts to develop a list of highly qualified candidates for this peer review. After carefully reviewing the candidates' expertise and credentials, as well as their conflict-of-interest status, ERG selected five peer reviewers. Appendix A lists their names and affiliations.

1.2.2 Activities Prior to the Peer Review Meeting

Several weeks prior to the meeting, ERG sent the five peer reviewers a copy of the draft Approaches Document, *Supplementary Guidance for Conducting Health Risk Assessments of Chemical Mixtures* (EPA 2000), and the peer review charge (provided in Appendix B). ERG also provided the peer reviewers with copies of public comments that EPA received on the Approaches Document. The peer reviewers each read the review document and, working individually, prepared a list of key issues (provided in Appendix C). ERG held an orientation teleconference with reviewers to clarify the charge and answer any questions about the review purpose and format.

1.2.3 Activities at the Peer Review Meeting

The five peer reviewers and 14 observers attended the peer review meeting, which was held at EPA/NCEA in Cincinnati, Ohio, on May 25–26, 2006. The peer review meeting was open to the public, and the meeting dates and times were announced both on EPA's project Web site and in the Federal Register. Appendix D lists the observers who confirmed their attendance either at the registration desk or over the telephone. The agenda for the peer review meeting is provided in Appendix E.

The peer review began with introductory comments and opening remarks by the meeting's facilitator (Jan Connery, ERG) and EPA:

- *Welcome and Introductions. Ms. Connery welcomed the peer reviewers and observers to the meeting, stated the purpose of the peer review, and explained the peer review process. She explained that each reviewer had been assigned the responsibility to prepare a summary of discussions for particular charge questions and that the reviewers would work together on the second day to review each others' drafts and prepare the final summary of discussions, conclusions, and recommendations. Ms. Connery also referred all observers to materials available at the meeting registration desk, including copies of the agenda and charge questions. The peer reviewers then introduced themselves and stated their areas of expertise.*

- *EPA Background Presentation. Linda Teuschler, EPA NCEA, spoke briefly on the Approaches Document. Slides for her presentation are included in Appendix F. The document presents concepts and methods that can be used to conduct CRAs (defined as "an analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors"). She explained the three triggers, five data elements, and eight steps to conducting a CRA. Dr. Teuschler clarified that the Approaches Documents is not a regulatory document, nor is it an official EPA guidance document. It also does not address biological or physical stressors. She acknowledged that the document is largely a compilation of existing risk assessment guidance, data, and risk information. She highlighted a few unique features, including the Cumulative Risk Toolbox and the idea of grouping chemicals for risk assessment based on exposure characteristics and toxic endpoints. Dr. Teuschler also described the document's organization, history, and next steps.*

- *Observer Comments.* The agenda included one time slot for observer comments. Ms. Connery opened the floor for observer comments; however, none of the observers present in person or by phone wanted to comment.

Following these opening presentations, Dr. Kannan Krishnan (University of Montreal), a peer reviewer and the designated chair of the meeting, opened the technical discussions among the reviewers to answer the charge questions. The technical discussions were strictly among the peer reviewers, with EPA occasionally answering questions of clarification posed by reviewers. The peer review meeting concluded with a writing session, during which peer reviewers prepared written summaries of their responses to the individual charge questions and developed conclusions and recommendations. All drafts prepared by individual peer reviewers were fully reviewed and vetted by the group. These summaries are included in Sections 2 to 8 of this report.

1.3 Report Organization

The structure of this report reflects the charge questions, organized by chapter. Section 2 summarizes the reviewers' general impressions of the document as conveyed at the beginning of the meeting. The sections that follow present responses to specific charge questions. All references cited in the text are presented in Section 9. The appendices to this report contain the following:

- List of the peer reviewers (Appendix A)
- Charge to the reviewers (Appendix B)
- Pre-meeting issues identified by reviewers (Appendix C)

- List of registered observers (Appendix D)
- Agenda (Appendix E)
- Slides of the presentation by Linda Teuschler (Appendix F)

2.0 General Impressions

To kick off the peer reviewer discussions, Dr. Krishnan asked each reviewer to describe his or her general impressions of the Approaches Document.

Dr. Krishnan began by saying that, in his opinion, even though the Approaches Document is not a regulatory guidance document, it does provide a unique (but not entirely new) focus on multiple chemicals, sources, routes, and timeframes. He thought that the document was clear and well-written and displayed critical thinking related to the new concepts and tools. It is a step in the right direction for probabilistic risk assessments, population-based assessments, and exposure time and effects. Dr. Krishnan did, however, have a number of concerns that he said he would address in the chapter discussions.

David Carpenter, University of Albany, also thought that the document was well-written, thoughtful, and emphasized how complex CRAs are. Though he found the document to be useful in raising awareness about the difficulty in evaluating all possible exposures and health outcomes, he was not convinced that it would actually impact how risk assessments are performed.

Paul Chrostowski, CPF Associates, Inc., also thought that the Approaches Document was well-written and remarked that he had enjoyed reading it. He said that the document is a “leap forward” for community-driven assessments. This document transcends programs and integrates guidance across programs. Dr. Chrostowski expressed concern over the complexity of the process, and questioned the applicability for very large risk assessments (e.g., ones that are evaluating 250 chemicals, 12 exposure groups, and 10 exposure pathways). Dr. Chrostowski also commented that it is a challenge to integrate risk assessments and public health assessments.

Jim Carlisle, California Environmental Protection Agency, said he found the document to be unusually well-written and readable. He commented that his initial thoughts were that the document was not specific enough because he was reading it as a guidance document. However, once he realized that it was not a guidance document, but was encouraging people to consider assessments they might not have done before, Dr. Carlisle had a more positive view.

Nga Tran, ExPonent, Inc., agreed with the other reviewers and recognized the tremendous challenge of linking the public health approach with risk assessment. She commended EPA for their attempt; however, she felt that the document needed to do a better job of explaining how to make sense of the results and of describing in what situations the approaches apply.

3.0 Chapter 1. Introduction to Cumulative Risk at the U.S. EPA

3.1 Charge Questions and Responses

Comment on the level of detail in the Chapter, specifically on its adequacy in citing and explaining currently available methods and guidance for assessing multiple chemicals, exposures and effects. What other relevant guidance related to exposure and toxicity combinations needs to be cited? Provide citations for any other significant materials or reports that need to be included in the document.

Comment on the adequacy of the Chapter to set the stage for subsequent discussions of expanded and new approaches in Chapters 3 through 5.

Comment on the scientific rigor of the information presented in the Chapter, specifically discussing the logic and description of the cumulative risk approach.

The level of detail in Chapter 1 is generally adequate. Much of this information is covered elsewhere.

Health endpoint (population illness) as the trigger for CRA: health effects have multiple risk factors and the process of attributing risks is often complex. In the context of this multi-factorial risk perspective, the process of evaluating the possible role of chemical exposures as one of many health endpoint triggers needs to be discussed. The CRA framework, as laid out in this document, is driven by source/chemical groupings, at least as a starting point, and much of the cumulative concepts are screening level assessments. Therefore, it is unclear what options are being suggested when health endpoints are triggers.

Different triggers will require different types of investigation; this should be more clearly differentiated in the document. Investigators should not assume chemicals are the cause of a health concern. When a health concern is the trigger, the investigation needs to connect cause and effect. It becomes more of an epidemiological investigation, involving differential diagnosis. When the trigger is a particular source, environmental concentration, or biomonitoring result, the investigation may more closely resemble a risk assessment. More distinction should be made between prospective and retrospective investigations. The quality and quantity of evidence to trigger an investigation should be discussed.

Cancer slope factors based on all cancers are unlikely to accurately predict occurrence of a specific type of cancer in a population.

Some panelists are concerned that the document makes too sharp a distinction between threshold and non-threshold effects. Some kinds of toxicity traditionally considered to be threshold events may in fact have thresholds much lower than previously believed and possibly below background exposures. For these types of effects, there may be no practical threshold. Endocrine and neurobehavioral effects may be in this category. Conversely, some non-genotoxic carcinogens are likely to act by a biochemical mechanism or pathway that would not produce cancer if the dose is below the dose required to trigger the biochemical or physiological event.

The benchmark dose (BMD) approach may allow for alternatives to the hazard index (HI) and margin of exposure (MOE) approaches. The BMD approach may allow for a probabilistic approach at dosages within or close to the observable range. Extrapolation to doses much lower than the BMD is not justified, however.

Biomonitoring should also be considered as a trigger for an investigation.

Limitations of earlier documents should not be portrayed as a weakness. They reflect the state of the science at that time.

3.2 Recommendations

The panel recommends that response additivity (the addition of dissimilar responses) be applied only to carcinogens, and only to those that act by a non-threshold mechanism. Figure 4-1 implies that response additivity applies to all mixtures of toxicologically independent chemicals. Section 4.5.1 and equation 5-4 seem to provide a basis for response addition to estimate an overall risk of an adverse effect from exposure to a mixture of non-carcinogens.

The concept of response additivity makes sense for carcinogens that are assumed to exhibit a linear relationship between dose and cancer risk (i.e., there is still a small probability of a cancer even at very low dosages) because probabilities for independent events are additive. However, for adverse effects that are thought to exhibit a threshold, risk management efforts would normally mitigate the exposure to a level below the toxicologic threshold so that the probability of experiencing each adverse effect would be virtually zero and the combined probability would also be virtually zero. The response additivity paradigm adds complexity, but no value, to non-carcinogen and threshold risk assessment. This does not apply to dose additivity.

Clearer definitions of response additivity and dose additivity should be incorporated into the document.

4.0 Chapter 2. Initial Characterization of the Population and Chemicals of Concern

4.1 Charge Questions and Responses

Comment on the level of detail in the Chapter, specifically on its adequacy in citing and explaining currently available methods and guidance for assessing multiple chemicals, exposures and effects. What other relevant guidance related to exposure and toxicity combinations needs to be cited? Provide citations for any other significant materials or reports that need to be included in the document.

Chapter 2 is a background chapter which presents definitions of populations of concern, attempts to define which should trigger assessment of exposures on the basis of health effects, and identifies which factors should trigger an exposure assessment. The relatively short chapter does contain appropriate detail in describing EPA's approach for assessing multiple chemicals, exposures, and effects. It is in general well-written with suitable references. There are few new or innovative ideas in this chapter, but given its purpose that is not specifically a criticism.

One notable lack is citations of the recent series of Toxicological Profiles for Chemical Mixtures produced by the Agency for Toxic Substances and Disease Registry (ATSDR). Only one of these (the one dealing with arsenic, cadmium, chromium, and lead) is even in the reference list. While these profiles deal with specific mixtures, and thus have a quite different goal than does the present document, they should be cited and noted, if for no other reason than to demonstrate that different federal agencies are at least aware of related activities. While this reviewer is not aware of documents from the other federal agencies (e.g., National Institute of Environmental Health Sciences [NIEHS] and the Centers for Disease Control and Prevention [CDC]) on the subject of mixtures, both have organized meetings that may have produced reports that could be mentioned. The European Union (EU) and the World Health Organization (WHO) also have publications and policies that should be acknowledged. This is understandably an EPA-centric document, but would benefit by at least acknowledging interests of other national and international agencies.

Comment on the adequacy of the Chapter to set the stage for subsequent discussions of expanded and new approaches in Chapters 3 through 5.

Chapter 2 does set the stage for subsequent discussions, and does this relatively well for Chapters 3 and 4. However, it is less successful for Chapter 5, as discussed below.

The population of concern obviously depends on the situation, and can be anything from all residents in an area to a subpopulation based on exposure, genetic susceptibility, age, cultural habits, economic status, etc. The document appropriately states that risks should be calculated separately for different populations, but does not clearly state that health risks from exposure should be determined based on the most vulnerable population.

The document distinguishes three different triggers for an exposure assessment: one triggered by health endpoints in a community, one triggered by elevated concentrations of a chemical in a community, and the situation where there are local potential releases of contaminants even in the absence of documented health effects or concentrations of specific chemicals. The mere potential for releases can trigger concerns within a community that may sometimes justify an exposure assessment. Regarding the population, the document lists three criteria for chemical selection, including the possibility of contribution to health effects already existing in the population, likelihood of exposure, and potential for overlapping exposures to similar or interacting substances. This list should certainly also include an elevation in rates of an unexpected disease in the population, as well as the community perception of elevated disease. This is a particularly important consideration, directly related to “community involvement.”

Communities probably have the most to bring to the risk assessment process through identifying diseases and exposures they perceive to be elevated in their community, whether they really are elevated. But their concerns need to be considered. There is also some lack of clarity with regard to subgroups of the population. If there is a need for a cumulative risk characterization in a population that is triggered by consideration of a subgroup, it is important that the whole population be the basis of the study. Exposure will rarely be limited to a subgroup. Some of the sensitive subpopulations mentioned, such as pregnant women, are too narrow in definition, since especially for more persistent substances, the sensitive period includes the time prior to pregnancy, which are often periods of decades for very persistent substances.

Regarding the chemical(s) of concern, the important considerations listed are toxicity, amount, interactions, persistence and/or ability to bioaccumulate or migrate, and potential for high exposure to sensitive populations. This list, however, does not include such important considerations as exposure of very large populations to chemicals of lower toxicity, which on a population basis may result in greater morbidity. There are suggestions that prioritization of chemicals of concern (and routes of exposure to these chemicals) should be done. While we recognize the utility of a screening tool for current practices in site assessment, this panel finds potential danger in prioritization too early in the evaluation, since often health effects become apparent due to chemicals and/or routes of exposure that had not been previously considered. Therefore, limiting the scope of the risk assessment should be delayed as long as possible.

There is no mention of the importance of biomonitoring as a trigger for risk assessment. Biomonitoring is a very important factor, as it is a powerful indicator of exposure. Of course it is more valuable for persistent than non-persistent substances, but has a role even in identification of exposure to substances that are relatively quickly removed from the body.

Biomonitoring also offers the possibility of distinguishing current from past exposures, and can predict future exposures. If persistent substances are found in human specimens but not in the local environment, this is an indication of past exposure. If persistent and non-persistent substances are present both in human specimens and the environment, this provides strong reason suspect ongoing exposure. Biomarkers of exposure, such as DNA adducts, may provide evidence of past exposure to non-persistent substances. Contaminants in the environment but not the human specimens may provide reason to search for future exposure. It is important to recognize that the mere presence of a contaminant in human specimens does not necessarily indicate an adverse health effect, but certainly does indicate that investigation of whether there is a health effect is appropriate.

Comment on the scientific rigor of the information presented in the Chapter, specifically discussing the logic and description of the cumulative risk approach.

The last section of Chapter 2 presents the conceptual model for CRA, and clearly acknowledges that this model cannot deal with all complexities. This is the limitation of the model, since what is needed is a model that does deal with all the complexities, however unrealistic this goal is. Areas that are underemphasized include the interactions between traditional EPA concerns (e.g., chemicals from waste sites) with chemical household exposures *via* such media as food and cleaning products.

While there is a degree of scientific rigor in the information presented, there is a lack of a comprehensive inventory of factors that contribute to risks and to the perception of risks in a community. Figure 2-4 shows these interrelations diagrammatically. Contaminant exposure may come from hazardous wastes, and exposure may occur *via* ingestion of contaminated soils, locally grown food, or drinking water; inhalation; or dermal absorption. But there is also contamination through commercial food and *via* use of household products such as cleaning agents and deodorants; volatile organic compounds, formaldehyde, and other chemical releases from carpets, furniture, and insulation; other contaminants in indoor and outdoor air; and other contaminants in drinking water. In many populations, especially those of lower socio-economic status, there are the confounding stresses resulting from poverty, unemployment, family

dysfunction, and violence, and the health hazards resulting from poor diet, obesity, smoking, excessive alcohol and/or drug use, and inadequate access to health care. These combined stressors lead to a sense of hopelessness. These factors may combine to lead a community to blame their problems on an exposure which may or may not be a contributing factor. While recognizing that EPA has focused this document on chemical exposures, not social factors, these other factors cannot be ignored. The social factors may often be the primary basis for a community-based request (or demand) for a risk assessment.

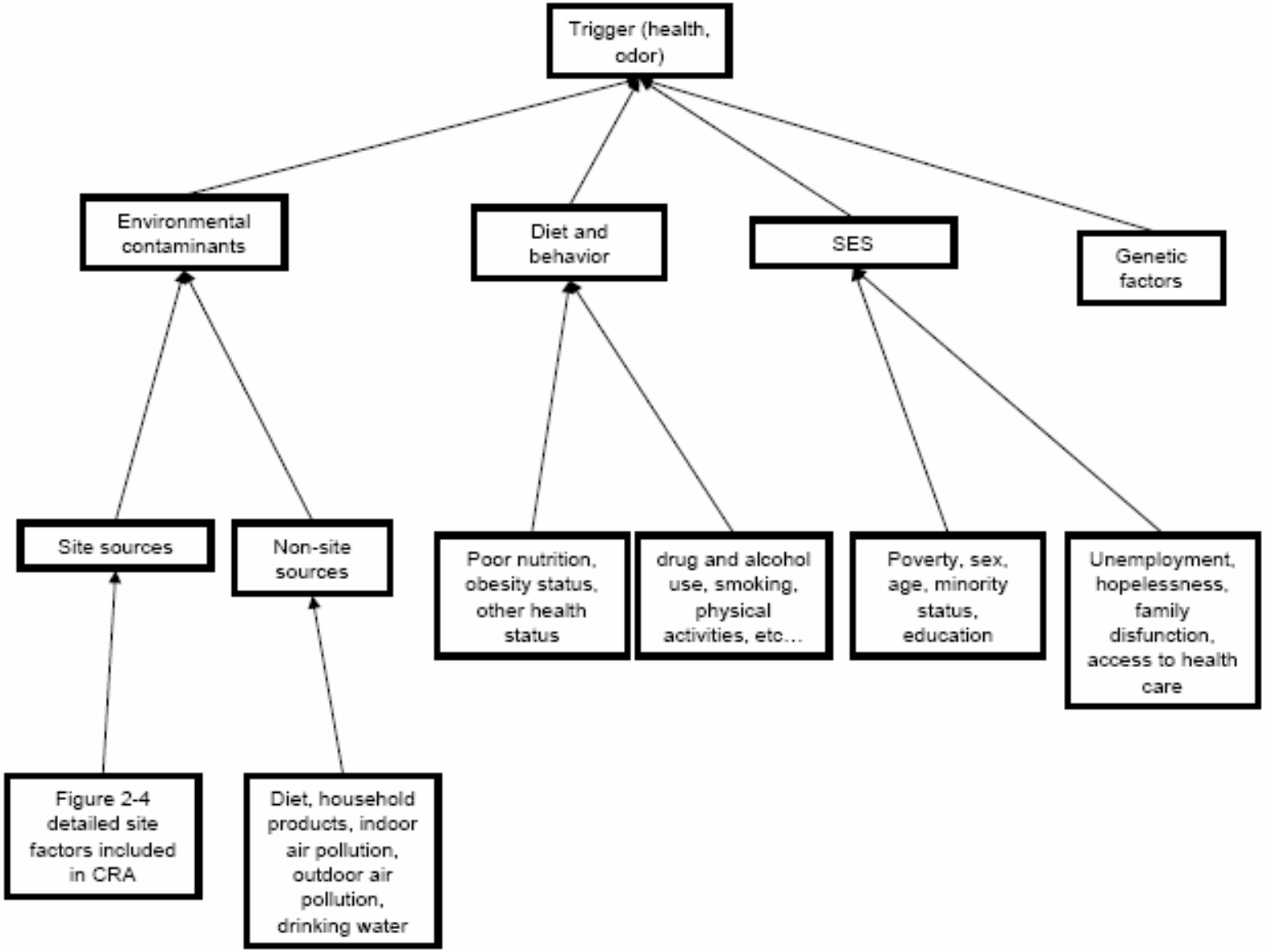
There is less success in having Chapter 2 set the stage for Chapter 5 than is the case for the other chapters, in that the structures are not parallel. One possibility would be to move up Figure 5-2 to Chapter 2, and redirect the discussion around the excellent points made in this figure.

4.2 Conclusions

Chapter 2 is well-written and covers most of the information needed for the rest of the document. It would benefit from better integration with the materials in the later chapters, especially Chapter 5.

4.3 Recommendations

Modest revision is needed for the purpose of better integration of this Chapter with the rest of the document. The panel recommends adding an additional figure to Chapter 2 (see figure on next page), with the further suggestion that a version of one figure currently in Chapter 5 (Figure 5-2) be included in Chapter 2.


Trigger (health, odor)
Environmental contaminants
Diet and behavior
SES
Genetic factors
Site sources
Non-site sources
Poor nutrition, obesity status, other health status
drug and alcohol use, smoking, physical activities, etc…
Poverty, sex, age, minority status, education
Unemployment, hopelessness, family disfunction, access to health care
Figure 2-4 detailed site factors included in CRA
Diet, household products, indoor air pollution, outdoor air pollution, drinking water

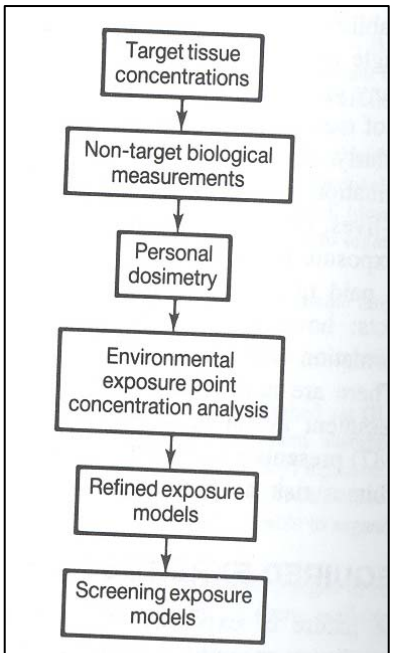
5.0 Chapter 3. Cumulative Exposure Assessment

5.1 Charge Questions and Responses

Comment on the logic and scientific rigor of the information presented in the chapter.

Although overall Chapter 3 was of good scientific quality, there were several areas where improvement would be important. EPA should spend some time, either in this chapter or in an earlier chapter, defining the goals of the exposure assessment, especially those that are concerned with accuracy and sensitivity. The resources to perform the exposure assessment should also be considered in terms of levels of human expertise, laboratory needs, and computational needs. Most people recognize that a regulatory exposure assessment may have goals that are dissimilar to those of a public health exposure assessment. Linking the goals to the triggers might be one way to accomplish this type of a goal statement.

Many assessors recognize that there is a hierarchy of exposure assessment techniques that yield different degrees of accuracies depending on the proximity of the exposure metric to the target organ. An example of such a hierarchy is given in the text box to the right (from Chrostowski 1994). The chapter emphasizes modeling almost to the exclusion of measurement or monitoring. Most exposure assessors believe that measurements, especially biomonitoring measurements, are the gold standard with modeling running a distant second. Chapter 3 should be expanded with a discussion of biomonitoring and biomarkers of exposure along with references to environmental monitoring methods. In discussing various modeling approaches, it was suggested that models should be viewed as examples, not preclude other approaches. Data quality and feasibility to support various levels of models should be discussed. EPA should consider integrating concepts from Food Quality Protection Act (FQPA) models. The chapter also needs a discussion of retrospective dose reconstruction when health outcomes are observed. If models are going to be relied on to such an extent, a discussion of validation, verification, and calibration should be included. These concepts should be linked to assessment goals and desired accuracy.



Hierarchy of exposure measurements.

Comment on the usefulness of these approaches to risk assessors who are interested in assessing multiple chemicals, exposures, and effects.

It would probably not be feasible at this time to undertake a large multiple chemical, multiple pathway, multiple receptor risk assessment using the methods described in Chapter 3. Such an assessment would be extremely resource-intensive. As the scales of the problem decrease (smaller populations, smaller geographical distances, limited number of chemicals, sources, and pathways), the material in this chapter becomes much more useful.

Based on your knowledge of the field, describe the extent to which the methods are new and innovative or, conversely, commonly known to risk practitioners. In your response, consider the combining of existing models or methods as an area of innovation. Note other methods, data or citations in the open literature that should be added.

The document did a good job of summarizing the state of exposure assessment at EPA—across programs and also from other agencies. In general, there is little in Chapter 3 that could be considered truly new, with the possible exception of the grouping concept and the proposed coordination between exposure assessment and dose-response assessment. It is difficult to put things in the context of a general state of knowledge of risk practitioners due to variability on expertise, education, and focus of risk practitioners. Many risk assessments, for example Superfund contaminated sites risk assessment following Risk Assessment Guidance for Superfund (RAGS), are performed by people without academic risk assessment backgrounds. These assessments have become so standardized that a knowledge of the practice of risk assessment is not needed to adequately perform an assessment. Others function at a more thoughtful level, performing assessments outside of individual programs, across program boundaries, assessing impacts of new chemicals or unusual pathways. This document should be useful to the higher end risk specialist to help synthesize material from various sources and across programs. The document is likely to be of little utility to those who only perform routine risk assessments. The sections of the toolbox relevant to exposure assessment are excellent. Although it is recognized that this toolbox cannot contain all tools, it contains enough tools to get most jobs done by an experienced user.

5.2 Conclusions and Recommendations

Overall this chapter is a useful compendium of currently practiced exposure assessment methods. Integration of information from different EPA programs and integration of fate and transport and exposure is commendable. General recommendations are primarily related to answers to charge questions.

5.3 Specific Comments

Page 3-10 and Text Box 3-5 discuss sources of information about populations for susceptibility assessment. Normally, a survey developed specifically for the issue would be used to get information about the population whether it be used for susceptibility or to develop population-specific exposure factors.

Page 3-11 raises the question of default receptors compared to actual receptors. The selection and characterization of receptors may depend on the goal of the exposure assessment. If regulatory, defaults may be appropriate. If health effects based, real data are needed.

Page 3-14 stresses that chemical transformation is a critical component. To a large extent, however, chemical transformation is site-specific. The document should include at least citations to works that integrate site-specific information into chemical degradation evaluations (e.g., BIOCLOR users manual).

Text Box 3-6 is quite elementary (as are the notes for Table 3-1) and may not be consistent with the rest of the chapter.

Table 3-1 (and other tables in this chapter to a lesser extent) summarizes chemical transformation information for a group of chemicals often found at Superfund sites; however, it is unclear how this information is to be used. Is EPA espousing these values as definitive or defaults? There is substantial literature regarding values such as these, for example Mackay et al.'s 5-volume series *Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals* (Lewis Publishers), Howard's 5-volume *Handbook of Environmental Fate and Exposure Data for Organic Chemicals* (Lewis Publishers), etc., that present numerous values for fate and transport parameters that may or may not correspond to the values in Table 3-1. How should the Table 3-1 values be viewed in light of the literature? Additionally, many of the entries on the table are incomplete or site-specific. Some are implausible, such as a single value Kow for "PCBs" (polychlorinated biphenyls). As an example of incomplete and site-specific information, dichlorodiphenyldichloroethane (DDD) and dichlorodiphenyldichloroethylene (DDE), which are cited as degradation products of dichlorodiphenyltrichloroethane (DDT), are only two of over a dozen metabolites of DDT and may be insignificant metabolites in some situations. The concept of half-life has only limited applicability in the natural environment and its use should be highly qualified. Half-life is only useful if the reaction order is known and invariant over the problem area. The panel suggested that Table 3-1 either be deleted or put in context with the appropriate reference.

Tables 3-7 and 3-8 need more explanation as to why the exposures are so different between chemicals when the initial concentrations are the same. For example, the maintenance worker's daily ingestion dose of mercury from site soils is 5 times that of arsenic, 13 times that of lead, and 50 times that of chromium.

On Figures 3-9 and 3-10, definitions for "TEM" and "DBP" are not included. "PK" (pharmacokinetics) and "TK" (toxicokinetics) are used somewhat interchangeable throughout the document when there is no apparent difference in meaning. Toxicodynamics appears in the definition of pharmacokinetics on page 7-7. Toxicokinetics is probably the intended word.

Page 3-23 states that it is important that "mass be maintained." Presumably this refers to conservation of mass (2nd law of thermodynamics). If accuracy is desired, this is mandatory. Although models may not explicitly conserve mass, post-processing may be used to accomplish this.

On page 3-26, currently only dioxins (polychlorinated dibenzo-p-dioxin/polychlorinated dibenzofuran [PCDD/PCDF]) have been adequately discussed by EPA regarding fate and transport. Even this is incomplete (disproportionation, metathesis). No other common complex mixtures (e.g., polybrominated diphenyl ethers [PBDEs], PCBs, toxaphene, or chlordane) have received sufficient attention to look at differential fate and transport of mixture components. It is questionable if this approach will ever have great utility for anything other than dioxins.

Although Figure 3-3 shows target tissue doses, it does not show any way of directly getting there, such as with body burden measurements.

On page 3-29, it is unclear how the grouping concept will facilitate exposure assessment. With very few exceptions (i.e., o- and p-xylene), chemical behavior is sufficiently different to warrant treating chemicals as distinct entities rather than groups. To extend the example, m-xylene is

sufficiently different to be separated out of the group of “all xylene isomers” and would be even less appropriately assessed in a group of “all methylated aromatics” or “all substituted aromatics.” Although grouping according to physicochemical characteristics may have pitfalls, grouping based on co-occurrence or temporality might be more useful.

In Table 3-3, EPA probably means “advection,” not “convection,” and “diffusion,” not “dispersion.” Convection normally has a thermal basis, whereas advection can mean any mass transfer. Dispersion serves to dilute concentrations, but diffusion is the movement of a chemical under a chemical concentration gradient driving force.

Chemicals rarely obey the simple rules presented in Table 3-6.

In Figure 3-5 on page 3-43, the numbers or units are not reasonable with respect to degradation rates. It is unreasonable to think that 100 parts per million (ppm) tetrachloroethylene (PCE) would decay to not detected (ND) in 10 minutes. This should be checked.

On page 3-51, why are “community-specific” exposure factors preferred? Why are individual factors not preferred?

On pages 3-54 through 3-58, although it has a strong theoretical basis, the calendar approach may be difficult to implement in a big assessment. EPA should consider the amount of resources to be expended on the assessment and if the goals of the assessment warrant the use of these resources.

The math requirements for time-dependent models are orders of magnitude greater than steady state models. In addition, time-dependent models are not amenable to a spreadsheet approach and must be written in a programming language or solved using special macros. On the other hand, only time-dependent models can yield a truly accurate calculation of chemical fate and transport. The need for accuracy should be weighed against the availability of resources.

What would be done with exposure data from physiologically based toxicokinetic (PBTK) modeling like in Figure 3-10? Since most toxicological dose-response parameters are based on administered dose, internal dose may not be a useful outcome of exposure modeling.

On page 3-79, “uncertainties related to air modeling are thought to be acceptable when considering high cost of monitoring” is a value judgment and probably not an accurate one. Accurate air modeling is also expensive. In many cases, more than 1 year of site-specific meteorological data are needed for good air modeling. Air models developed for Clean Air Act (CAA) compliance and permitting and not for exposure assessment have deficiencies in exposure assessment use. For example, predictivity of wet deposition is poor with even the most refined model. Screening models are likely inaccurate by a factor of 10 or more just due to their architecture and performance specifications. If coupled with other uncertainties such as those in emission rates, extreme meteorological events, and averaging times, screening models may be inaccurate by several orders of magnitude. This is again a balancing act between accuracy and resources, but air modeling should never take the place of air monitoring.

On page 3-89, the second sentence is long and confusing and should be broken up.

There is no discussion of probabilistic exposure assessment or related concepts involving use of stochastic principles. Given that EPA programs rely heavily on probabilistic concepts, this topic should be integrated into this chapter with citations to Agency probabilistic risk assessment documents (e.g., *Risk Assessment Guidance for Superfund Volume 3 Part A: Process for Conducting Probabilistic Risk Assessment* [EPA 2001]). Attention should be given to parameterization of probabilistic models.

There was a substantial amount of discussion regarding screening out chemicals. Although some of this discussion may be more relevant to other chapters, it was generally felt that high toxicity or high mass chemicals should not be screened out on the basis of exposure. With regard to the information on page 3-50, it was suggested that a CRA keep documented exposures in the risk assessment, until proven unimportant. It was noted that some regulatory programs have specific screening techniques that are useful within the goals of these programs.

In Table 3-6, association with a single compartment might be opposed to multiples concepts.

Figure 3-10 is a good example of relations of different dose concepts.

In several places, the chapter needs stronger statements that children are more vulnerable.

On page 3-60, other considerations in addition to source of fish are also important regarding mercury in the diet.

The chapter needs a discussion of chemical-chemical interaction in the environment and how it can be assessed in a CRA.

Some panelists felt that there was insufficient emphasis on dermal exposure.

6.0 Chapter 4. Cumulative Toxicity Assessment

6.1 Charge Questions and Responses

Comment on the logic and scientific rigor of the information presented in the Chapter.

Comment on the usefulness of these approaches to risk assessors who are interested in assessing multiple chemicals, exposures and effects.

Based on your knowledge of the field, describe the extent to which the methods are new and innovative or, conversely, commonly known to risk practitioners. In your response, consider the combining of existing models or methods as an area of innovation. Note other methods, data or citations in the open literature that should be added.

The document proposes to group chemicals by co-exposures and common effects for analysis using chemical mixtures risk assessment methods. Considering chapters 3 and 4:

> *Describe the usefulness of this approach to handling multiple chemicals, exposures, and effects.*

Discuss the logic and transparency of the approach, highlighting any inconsistencies or needed improvements in the approach.

Once the chemicals are grouped, comment on the clarity of the procedure regarding next steps, i.e., the application of chemical mixtures risk assessment methods for dose-response and risk characterization.

The document emphasizes the need for cooperation and iteration between the exposure and toxicity assessment processes. Comment on the scientific basis for cooperation and iteration between exposure and toxicity assessments, providing your opinion on the need for this concept to be emphasized in the document.

Chapter 4 presents the tools and concepts relating to multi-route exposures, evaluation of secondary and tertiary effects, as well as toxicological interactions. The aspects relating to the consideration of local versus systemic effects, time course of effects versus exposure in context of mixtures, and HI based on lower confidence limit on BMD (BMDL) are spelled out nicely and clearly for practitioners.

The idea of changing dose-response analysis so that it occurs concurrently and iteratively with exposure assessment, while scientifically sound, will have major implications for the way EPA (and other organizations) does business. Such a major structural change needs careful thought and consideration of all the implications. Currently, dose-response analysis typically occurs independently of site investigation and analysis. It is typically done in a highly controlled and structured manner, with input and peer review from many sources. For example the health criteria in the Integrated Risk Information System (IRIS) database criteria undergo extensive review before becoming final. To do this on a case-by-case basis would be exceedingly resource intensive. It is difficult to imagine that the same level of review and scientific consensus-building would go into a site-specific analysis.

6.2 Recommendations

The categorical regression as a method of analysis in CRA is described without sufficient details. It is important to provide a better description of the approach as well as the reasons for suggesting the use of categorical regression for CRA. An appendix describing this approach along with an example of application to mixtures, may be included.

There is no discussion of using physiologically based pharmacokinetic (PBPK) models in the process of computing a cumulative hazard index (CHI). Since the exposure chapter emphasizes the use of these models to get at internal dose estimates, it is important to specify in Chapter 4 ways and means of using internal dose in computing HI. Publications by Haddad et al. (2001) and Dennison et al. (2003) are relevant in this context. The document should include approaches that allow the use of internal dose in CRA.

The document does not clearly present ways of computing the interaction magnitude for modifying the HI. The default value (5) appears to have originated from some previous work conducted by EPA (see pages 4-42 and 4-43). The magnitude (default value of 5) presumably depends on the mechanism, end-point, etc., and this aspect should be clarified.

The definition of secondary effects, for use in computing target organ toxicity dose (TTD), is problematic. Page 4-24, lines 3-6 suggest that effects mediated by metabolites and non-adverse effects may be considered secondary. These statements are incorrect and should be deleted.

The document makes no reference to the use of current knowledge on genetic epidemiology in the context of CRA. This obvious deficiency should be fixed.

Section 4.4.1 on chemical grouping should have a simple schematic presenting the various levels of information and confidence associated with them (e.g., target organ, mode of action, mechanism of toxicity, reception interaction, quantitative structure-activity relationship [QSAR]).

6.3 Specific Comments

The concept of response additivity makes sense for carcinogens that are assumed to exhibit a linear relationship between dose and cancer risk because the cancer risk is expressed as a probability, and probabilities for independent events are additive. Whether it is also applicable for non-threshold systemic toxicants (e.g., lead-induced neurotoxicity) should be clarified. Similarly, response additivity does not make sense for threshold carcinogens (i.e., non-genotoxicants).

The time-related issues in dose-response assessments should be addressed (e.g., 8-hour exposures versus calendar-based exposure data; see NRC 2004). An alternative to concurrent dose-response analysis is to employ “look-up” criteria as we have now, but to generate criteria for more time points such as acute, subacute, and subchronic. Even this scaled-down approach will require a major effort to “mine” existing data or generate new data to develop a time-dependent toxicity database to be used in conjunction with time-dependent exposure information. Most long-term toxicity studies have only a terminal sacrifice or at most that plus one interim sacrifice. Data recorded on a more frequent basis are limited. Thus, for many chemicals, time-to-effect data will be difficult to come by unless new studies are completed.

There is a level of complication concerning contaminant metabolites that are not considered (e.g., when a metabolite has a different and sometimes even an opposite action from the parent; see page 4-12). This is the case for some parent PCB congeners and their metabolites, in that the parent may be anti-estrogenic but the metabolite is estrogenic (Gierthy et al. 1997). This problem complicates the relative potency factor (RPF) approach (see page 5-11), although the problem is certainly acknowledged. But as we learn more about mixtures even of chemicals of the same general class (e.g., PBDEs, dioxins/furans, PCBs, and toxaphene) we find that each congener has its own profile of biological actions, and often two congeners of the same class can have totally different and even opposing actions. This problem is also relevant to the discussion of the CHI (see pages 5-15 and 5-16).

There needs to be greater consideration of actions of chemicals and mixtures that are indirect (see page 4-16). For example, dioxins stimulate enlarged livers, and the livers then may do a variety of things that have nothing to do with the induction of P450s, such as cause elevations in fasting glucose levels or increase the synthesis of cholesterol and other lipids. Often these effects are not appreciated even as possibilities until demonstrated in animals or people.

If no-observed adverse-effect levels (NOAELs) and target organs for CRA can be obtained from the IRIS database, then it would authoritative. However, lack of data for certain chemicals that are part of the assessment might represent a problem. This caveat should be acknowledged and applicable approaches may be identified. In essence, how will toxicological data gaps be handled in the CRA?

This chapter needs to have some language regarding the confidence/uncertainty or the strength of data on secondary effects, since they may not come directly from an authoritative database such as IRIS.

There is also a concern regarding the severity of effects being added. For example, can you add an A-category carcinogen and a C-category carcinogen? Yes, but information for A is stronger than C. There is some old work that proposed weighting factors for severity of carcinogens (A, B, and C). Severity (e.g., pages 4-35 and 4-36) was previously used in the derivation of Superfund reportable quantities. How do these two methods compare? Can the TTD concept also be used for cancer endpoints?

When it comes to dose addition or response addition, a problem seems to arise when dealing with mixtures of chemicals that have reference doses (RfDs) or cancer slope factors (CSFs) and chemicals that are assessed by other means. For example, lead is usually assessed by biokinetic modeling, Clean Air Act criteria pollutants are usually assessed by comparison to an air quality standard and most other hazardous substances are assessed by means of RfDs. These dose-response metrics are not equivalent; however, some method needs to be developed to handle them additively. A similar issue could relate to mixtures of carcinogens where individual components are assessed by MOE or stochastic approaches.

Concerning chemical mixture grouping and the toxicity assessment scheme, the level of aggregation and resulting uncertainty about grouping methods should be discussed. For example, grouping based on common mode of action would be less uncertain than grouping based on common endpoints. Grouping based on structure-activity relationship (SAR) as an initial screening approach may also be suggested.

Page 4-30, it does not seem appropriate to designate an uncertainty factor (3) to account for the differential sensitivity of infants to mixtures. Presumably this is meant to be the interindividual variability factor.

Pages 4-23 and 4-27, the tables and figures on these pages list several target organs as both primary and secondary targets for the same chemicals. Primary target organs for these chemicals may be indicated by italicizing (the name of the chemical) in appropriate places.

Figure 4-12 suggests that internal dose-based dose-response relationships are route-specific. The contrary has been shown to be the case with a number of chemicals (e.g., vinyl chloride). Examples in the literature show that, for systemically acting chemicals, the internal dose based assessment allows the construction of a single dose-response relationship for all routes together (i.e., inhalation, oral, etc.).

In Section 4.7, lines 21–23, the only published reference on multi-route PBPK modeling of mixtures is Nong and Krishnan (2005).

7.0 Chapter 5. Cumulative Risk Characterization

7.1 Charge Questions and Responses

Comment on the logic and scientific rigor of the information presented in Chapter 5.

The logic and scientific information is derived based on the previous Chapters 1–4. While Chapter 5 is well-written, there are several considerations recommended for inclusion in this chapter. Trigger issues and scope of the CRA as they relate to Chapters 1 and 2 also need to be clearly summarized.

Comment on the usefulness of these approaches to risk assessors who are interested in assessing multiple chemicals, exposures and effects.

Approaches are useful, with the caveat that they are useful for what purpose and what question being answered. Whether they are useful depends on the context and whether information/data are available to implement it.

Based on your knowledge of the field, describe the extent to which the methods are new and innovative or, conversely, commonly known to risk practitioners. In your response, consider the combining of existing models or methods as an area of innovation. Note other methods, data or citations in the open literature that should be added.

The panel does not believe that the methods presented in the Approaches Document are new and innovative, with the exception of the application of categorical regression. The main contribution of the document is putting all ideas in one place, so readers can consider all possible options. Other options for assessing multiple health effects and harmonizing the characterizing cancer and non-cancer risks are noted in the issues/consideration section below (see Section 7.2).

Use of the compound and sophisticated models in this document introduces a great deal of uncertainty into the cumulative risk estimates. Does the document clearly delineate the sources of uncertainty introduced by this approach? Please provide guidance for developing a more comprehensive approach to characterizing the results of such models to address the many sources of uncertainty.

Chapter 5 adequately acknowledged the uncertainties associated with CRA. Section 5.4 could be expanded to further delineate the sources of uncertainties introduced by methods such as CHI, RPF, response addition, or categorical regression. Probabilistic approaches should be included to characterize uncertainties. It should be clear that there is not one single tool to characterize uncertainty. Model selection uncertainty and measurement uncertainty can be characterized by different tools. Uncertainty is going to be characterized adequately using a variety of tools, starting with sensitivity and then something more quantitative with more sensitive parameters.

Are the cumulative risk approaches in the document appropriate for addressing all types of health effects (e.g., cancer, neurological, behavioral, respiratory, etc.)? Which types of health effects are best addressed by them?

Most panel members did not understand the question. The panel is of the opinion that the same approach should be used for all kinds of health effects. One reservation is the fact that when health outcomes such as cancer and behavioral effects are triggers for CRA, the tools presented in this document are plagued with inappropriate assumptions/defaults, particularly if the question concerns exposure and disease association. However, the approaches identified in the document could be appropriate for hypothesis generation when health outcomes are triggers for CRA.

7.2 Additional Issues/Considerations

7.2.1 Risk characterization when health effects are triggers for CRA

Trigger factor should be a prominent part of the final risk characterization (indicated in Chapters 1 and 2). This was not addressed in the risk characterization chapter (Chapter 5) to the extent that is necessary, particularly for when health endpoint (e.g., population illness) is the trigger for a CRA. Very often, EPA or a private party must respond to complaints of health effects from the community, which wants to know if there is a link between chemical exposure and a health effect. In general, health effects have multiple risk factors and the process of attributing risks is often complex. An example that reflects this multi-factorial risk perspective concerns a native population whose principal diet is marine mammals and foods with high fat content (e.g., butter and high fat foods), with the majority of the population on food stamps, and a large number with alcohol, smoking, and a variety of lifestyle risk factors. The population has elevated heart disease that could be due to changes in diet and/or environmental exposures. Nevertheless, the community in this case focuses their concerns on environmental exposures. Oftentimes these complaints are addressed by a health study or a mini-epidemiologic investigation. When health endpoints are triggers for CRA, the analytic methods need to be in context of this multi-factorial risk perspective. While EPA should be commended for embracing the concept of a health endpoint as the trigger for CRA, the analytical approaches for exposure and dose response assessments as laid out in Chapters 3 and 4 are driven by source/chemical groupings, at least as a starting point, and many of the cumulative concepts are screening level assessments, laden with default assumptions. Given these analytic approaches, it is difficult to see how the risk characterization results can be interpreted in context of health effects with multi-factorial risk factors. This type of trigger may require traditional epidemiologic investigation in addition to CRA.

If health endpoints are the triggers for the CRA, there needs to be some way of associating the risk characterization results to the endpoints that are the triggers for the assessment in the first place. For example, how will the risk assessment be used to investigate a leukemia cancer cluster in a community? Will individual exposure factors be used? Will EPA be able to develop maximum likelihood estimation (MLE) (or age-specific, gender-specific) cancer slope factors?

A health-driven risk assessment also needs to deal with the concept of causation. EPA decisions regarding hazard identification are based on weight of evidence concepts rather than causation concepts. Community members will want to know if the emissions from the factory are causing the leukemia cancer cluster, not the upper bound probability of a hypothetical person contracting some kind of cancer. EPA might want to consider integrating concepts from classical causation (e.g., Bradford Hill 1965; Susser 1991) or evidence-based toxicology (e.g., Guzelian et al. 2005) to make risk assessment results more realistic.

7.2.2 Biomonitoring data as trigger for CRA

Biomonitoring data could be used as triggers for CRA. Typically, when body burden data are involved, the risk management question tends to relate to exposure reduction. Therefore, when biomonitoring data are triggers, complete CRA may not be necessary. Rather, exposure assessment to identify sources that contribute to the body burden would be the more appropriate analyses. Further, if cumulative risk characterization were to be carried out, it would also need to be based on dose-response information derived from body burden data. Chapter 5 should add a section to address cumulative risk characterization issues relating to biomarkers as triggers.

7.2.3 Screening level assessment versus detailed risk characterization should be given some thought in Chapter 5.

There is a hierarchy of exposure assessment (see comments on Chapter 3). Type of exposure assessment and accuracy goals conducted in exposure assessment should be revisited in Section 5.1 ("address multiples"). Page 5-9, lines 6–8 briefly address issues relating to grouping of chemicals and pathways, and alternative grouping of factors and possible double counting. This discussion should be expanded to discuss limitations and purpose of groupings in a CRA. For example, is the purpose of grouping only to narrow down the list of chemicals to be included in the CRA, is it meant to conduct a screening CRA, or as a way to look at fate and transport issues? What assumptions (worst-case) should be used? How should the results be interpreted and used? A discussion on the hierarchy of screening (grouping) approaches, sophisticated stochastic models to account for multiples (i.e., time, space, routes, and chemicals), and the data requirements should be added.

7.2.4 Grouping of endpoints and exposure.

The document has an extensive discussion in Chapter 3 on grouping of chemicals based on crude chemical factors such as log Kow and bioconcentration factors to narrow down the list of chemical of concern. A similarly crude approach of grouping based on SAR should also be discussed as a potential option to be used in conjunction with the exposure grouping in the initial ranking of chemicals for inclusion in a CRA.

7.2.5 Interpretation and uses of risk characterization results given the nature of CRA methodologies

A discussion of how the results of a CRA could be used is needed. Further, it would be extremely helpful to provide a summary of the types of CRA (e.g., from screening to refined/probabilistic approaches) that would be more appropriate for what triggers (e.g., health clusters, chemicals, or sources) and purposes (e.g., predict future or current risks, identification of intervention strategy, regulatory decisions, or determining exposure-effect association).

7.2.6 Time-related cumulative risk characterization

The focus on the spatial and temporal profile of exposures and risks in a CRA lead to the need to characterize risks for time intervals different from the traditional acute and chronic duration. As such, time-related dose-response will need to be developed. Assumptions used in a CRA when such dose-response data are not readily available should be addressed.

7.2.7 CHI or adding MOE's as a quantitative approach to cumulative risk characterization

CHI is provided as an alternative to the RPF approach. The risk-based toxicity value used in the calculation of hazard quotients (HQs) and CHIs are RfDs (see equation 5-1, page 5-12). The impact of uncertainty factors when RfDs are used needs to be further examined and discussed. The uncertainty factors (UFs) are not explicitly addressed under this approach. On the other hand, when aggregating MOEs (approach used under FQPA), UFs are explicit in the scaling of MOEs for addition. This point is missed in the discussion about adding MOEs in this section of the cumulative risk characterization chapter (see lines 3–15, page 5-15).

Interpretation of CHI (see page 5-13, lines 19–23) is somewhat challenging. If a CHI is slightly greater than 1 there might be some concern (i.e., CHI>3). But how does one interpret if the CHI is between 1 and 3? If the CRA was triggered by community health concerns, how can CHI numbers be used in context of these concerns? Does this approach fit this situation? All methods have limitations and are useful for different purposes. While this approach is appropriate for regulatory purposes to protect public health, assumptions and uncertainties embedded in this approach is problematic when trying to apply these results to explain health issues in a community. Chapter 5 should include a section to discuss limitation and interpretation of existing methods to characterize cumulative risk when health outcome is a trigger. While all risk characterization approaches described in the Approaches Document have utility, they are not of value for all situations.

7.2.8 Considerations to harmonize risk characterization of cancer and non-cancer effects

As the focus shifts from individual chemical and primary endpoint to multiple chemicals and multiple effects with emphasis on health endpoints and human receptors, the two distinct approaches of characterizing cancer and non-cancer risk present practical challenges in integrating and interpreting multiple risks. More specifically, while the public health impact in terms of increase in number of cancer cases can be readily estimated based on the results of a cancer risk assessment, the direct estimation of the public health impact based on the results of a risk characterization for non-cancer effects using the CHI approach is not readily transparent. The BMD approach offers an opportunity to estimate the probability of non-cancer effects (above biological threshold, if exist). Its application to harmonize risk characterization of cancer and non-cancer effects should be considered as potential options. Similarly, the ordinal regression method (see page 5-19, lines 14–15) offers some promise for a probabilistic approach to estimating toxicity from multiple chemicals. See comments on ordinal regression (Section 7.2.9).

7.2.9 Severity grouping and ordinal regression calculation for multiple effects and pathways

Ordinal regression for multiple health effects seems to be a reasonable expedited option to address multiple effects. While the panelists found no major problem with the method, some clarity on categorical regression in terms of its value in CRA is needed—specifically, how results can be interpreted in context of CRA when this method is used. For example, how does one interpret "adverse outcome" into public health impacts? What is the connection between

severity grade and clinical health outcome such as diabetes or myocardial infarction? A more detailed discussion on the interpretation of the outcome of the probabilistic and ordinal regression analysis should be presented. The panelists suggest that an appendix and an example be provided.

7.2.10 Another option to address multiple health effects other than severity grouping

The discussion to dismiss approaches to address multiple effects of concern due to difficulties in incorporating it into a risk management evaluation (partly due to the different effects having to be ranked in order of public health concern, see page 5-17) is too limited. There are neutral methods to rank/order public health impacts for risk management evaluation available, such as converting health impacts into disability adjusted life years (DALY). Options to expand the results of CRA to rank public health impacts explicitly should be provided. While this approach may be more arduous, it could be more explicit in addressing multiple health effects. Since this document is about identifying approaches, this alternative approach should be described and considered.

7.2.11 Examples of RPF method needs to be included in Chapter 5, section 5.2

Chapter 5 emphasizes CHI calculation and calculation based on categorical regression. There is no discussion or examples on response addition or RPF. Either clarify that only a couple of approaches are considered as examples or add a discussion in context of risk characterization, limitation, and interpretation about those other methods.

7.2.12 Risk characterization as an iterative process of ensuring compatibilities between the analytic methods, results, and CRA goals

Figure 5-2 on page 5-31 describes the risk characterization decision as an iterative process of revisiting the scope, analyses steps, and risk characterization results. It is a very useful process of ensuring that the analytic approaches and results are consistent with the CRA goals and the risk management questions that are being addressed with the CRA. This generic flow diagram should be displayed and discussed in detail upfront. Also, the descriptive factors that determine the level of “acceptability” of extrapolation, simplifications, and omissions should be described. Clearly, “acceptability” will be tied to the nature of the CRA goals (questions being answered with the intended CRA). This process will help focus the CRA goals/risk management questions and determine whether the methodology under consideration and available data/tools are appropriate.

7.2.13 Joint Toxicity—Interaction

Section 5.3.3 of the cumulative risk characterization discusses interaction and refers to Table 5-1 on joint toxicity. Based on the discussion in this section, it is not clear how this information is used, given the method of estimating joint toxicity described in Chapter 4 (Section 4.6.2, “A quantitative method for evaluating interaction effects”). Additional explanation of the relationship between this section and the approach described in Chapter 4 would be useful.

7.2.14 Data gap

EPA has derived toxicological data for only a small group of chemicals compared to the larger universe that people might be exposed to. How will toxicological data gaps be handled in the CRA and explained in cumulative risk characterization?

7.2.15 Uncertainty and Sensitivity Analysis

Quantitative uncertainty and variability analysis was mentioned in the document on page 5-25, but not further emphasized. The need to identify sources of uncertainties with greatest impact on the overall conclusions should be discussed. Probabilistic analyses should be further explored to quantitatively characterize the full range of uncertainty and variability.

How alternative grouping could effect cumulative risk characterization such as the CHI should be discussed. Also, clear reference should be made to the use of sensitivity analysis to evaluate the impact of alternative grouping methods.

7.2.16 Feasibility and data quality

Quality data input is an important consideration, especially when complex calendar models are used. A discussion on data quality and their appropriateness for the various CRA options would be helpful.

7.2.17 Risk communication

Risk communication is a major concern and undertaking when CRA is involved. There is particular concern about the interface between values calculated and incidence of disease in a real population. How are these risk numbers analogous to numbers generated in epidemiological studies? Some programs in EPA will take a cancer probability and multiply by the population to get a number of people. If, in a population of 100 people with a cancer cluster of 6 cases of leukemia, the CRA provides an estimated of 75 additional cases, how does one reconcile and communicate these vastly different estimates to allay fear?

7.3 Specific Comments

Figure 5-1 is unclear. The panel had difficulty understanding the arrows and axis of the three-dimensional depiction of cumulative dose over time, space, and multiple chemicals. This figure needs modification or more discussion. The total cumulative dose might not exceed the threshold. The risk arrow is confusing. There seems to be inconsistency with the duration of exposure (e.g., adults should have a shorter duration than the elderly, but they are on the same line of duration of exposure). The main confusion seems to be the different diseases depicted in the figure. The panel suggested that rather than specific disease endpoints, the figure should stay conceptual at the more generic and typical outcome of CRA (e.g., the line in front is representing chronic effects and the line in the back is acute). This diagram clearly demonstrates the challenge of communicating CRA results. It is also useful to have an example that detailed the exposure scenarios, chemicals involved, and specific health outcomes.

8.0 Overarching Issues/Questions

8.1 Charge Questions and Responses

What is the reviewer's overall evaluation of the scientific content, readability and utility of the entire document? Provide any suggestions relative to structure or content that would improve the quality of the document.

EPA's Approaches Document focuses on approaches and tools that facilitate the consideration of integrative multiples (i.e., multiple chemicals, multiple sources, multiple routes, multiple timeframes, and multiple effects) in the context of CRA. In general, the document is well-written, timely, and represents forward thinking in the complex area of CRA. It is not a regulatory guidance document and does not describe any methods and tools that are entirely new or novel. However, it does build on the current concepts and tools that relate to the consideration of issues relating to the "integrative multiples." The panel appreciated the population focus of this document even though there is concern about feasibility of applying the approaches and tools to really big risk assessments and complex scenarios. A particularly original aspect of this document is the manner in which the iteration and cooperation between the exposure assessment and toxicity assessment phases are emphasized and presented. However, the panel felt that the role and place of the various approaches should be clearly identified within the larger picture of CRA for source-based and health effects-based assessments. Even though the examples presented in the various chapters help clarify the applicability of the various tools and concepts in CRA, it is strongly suggested that the authors consider using an example that is carried all the way through the process. Thought should also be given to the inclusion and interpretation of biomonitoring data at all levels of the process.

It is unclear as to why the word "alternative" figures in the title of this document. Certainly, this is not the first or only time an EPA document presents more than one method. The word "alternative" in toxicology is often used to refer to *in vitro* and QSAR methods, which is not the case here. The panel strongly suggests that "alternative" be dropped from the title of this document.

In general, comment on how well the text in the document supports the ideas shown in the Figures. How should the examples be modified to adequately illustrate the concepts?

Overall, the figures are well done and the text is supportive of the ideas shown in the figures, with minor exception. These exceptions are identified in specific comments relating to each chapter (see Sections 3 through 7). A figure identifying hierarchy of exposure assessment should be added.

In general, comment on the consistency of the suggested approaches with current Agency guidance from a technical perspective. How, if any, does the population focus alter any existing technical procedures or assessment steps, including information requirements? Which existing EPA procedures or methods would be affected and in what manner? Specify any better examples and data tables that could be used to demonstrate feasibility of assessing multiple chemicals, exposures and effects.

The approaches outlined in the document are consistent with current agency guidance from a technical perspective, except for ordinal regression method, which has not been found in existing agency guidance.

The current agency guidelines do not address biomonitoring and internal dose. Therefore, if CRA is based on approaches that make use of these data, there will be inconsistency between CRA methods and current agency guidelines.

The focus on population in this document is different from the hypothetical receptors in the agency's current guideline methodology. The population focus in the Approaches Document is about "real" populations. If the CRA is done to predict risks for hypothetical target populations (as currently done) for risk management decisions, then approach/assessment steps do not change. However, if the CRA is done to address health questions raised by "real" populations (exposure and effects), then careful attention should be paid to the default assumptions that are embedded in the methodologies presented. *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (EPA 2005) is the most consistent with population-based CRA.

Information requirements will be high when moving beyond initial screening assessment, and when cumulative exposure and risks will need to be modeled, particularly moving into probabilistic type of models, time-relevant dose-response, etc.

Other considerations on how it would change existing procedures:

- It could change how background is dealt with.
- It should integrate information about other population risk factors and environmental justice considerations.

It is acknowledged in this document that employing worst-case assumptions for all pathways of exposure and health endpoints is unreasonable. What advice would you provide to EPA regarding a balanced approach for choosing assumptions for these cumulative risk models?

Risk assessments typically employ upper-end values for variation (population heterogeneity) and conservative values for uncertain parameters. This is well accepted and usually described in an uncertainty section. In cumulative assessments, this conservatism may be compounded. In an assessment of risk or hazard from a single source, possibly a single pathway, and a single chemical or a small group of related chemicals, the probability of an individual exceeding the estimated dose may be, for example, 5 percent. But for a multi-source, multi-media, multi-pathway, multi-chemical assessment, the likelihood of a single individual being maximally exposed from all the sources and media, by all pathways, and to all chemicals becomes much smaller—some would say vanishingly small. The panel suggests that either the level of conservatism be reduced for cumulative assessments, or at least the extra conservatism be acknowledged. A quantitative uncertainty analysis would be useful to identify the degree of conservatism. Distributions for exposure parameters would help to quantify this uncertainty. Mass balance needs to be maintained in order to ensure that upper-end exposures from multiple pathways are not compounded. This is more important in a detailed analysis than in a screening analysis.

To what extent does this document provide useful and practical information and advice for risk assessors who are faced with real world situations?

The community of risk assessors is diverse. Utility of this document will vary with the user. People who do routine risk assessments are not always risk assessors. Often times, routine risk assessment is a cookbook exercise with little judgment or critical evaluation of results. To the community of risk assessors doing more thoughtful risk assessments or people engaged in performing risk assessment research, the document is very useful. The panel learned a lot reading the Approaches Document and found it to be a very useful document. The document was also viewed as an incentive to advance the state of the art. The concept of CRA is considered to be important because existing assessments are too narrow in focus. The panel found the Toolbox to be very useful. The document could be made more useful with a continuing example.

Is the approach proposed likely to lead to realistic risk scenarios? What validation exercises would you suggest for the risk assessor? How might EPA demonstrate such a validation approach? Are their places in the document where real-world examples may provide utility? Can you suggest any desk-top exercises that might be used to evaluate the utility of the approaches described in this document?

This question also is related to Question 6d. The panel agreed that the degree of conservatism would be proportional to the complexity of the risk assessment. Thus, a highly complex CRA was not likely to realistically predict risk. Viewing the document as a model, three concepts are important to assessing the validity of the results—verification, calibration, and validation.

Verification determines whether the model works. Can one take a group of chemicals through the process and get the process to work? Do the linkages (e.g., between exposure and dose-response, and between dose-response and risk characterization) work out? Does implementation of the model yield a logical result? In order for the model to be right, one needs to compare the results of the model to a situation of known accuracy. If the model does not compare to results of known accuracy, calibrate the model. Change something about the model to make the results come out right. Validation is reserved for already accurate results. Calibration of an inaccurate model could involve changing exposure factors, chemical concentrations, toxicology, or scenarios. After the model has been calibrated, go to another situation and see if the model works for another scenario. If it works, the model is considered to be valid. The concept of evaluation, which is a lower level of assessment of model viability, was also introduced. In many cases, evaluation is all that is feasible. The charge question is really a combination of these things.

Considering the document as a model, does its application predict what is going on in nature? One should see whether the model corroborates known health effects and see whether perturbation of input parameters produce logical outputs. One example is of birth defects from exposure to disinfectant byproducts (DBPs). If the model accurately predicts the incidence of birth defects in a population exposed to DBPs, will a perturbation of the system (e.g. by removing dibromochloromethane [DBCM]) result in lower incidence? This raises questions about the ethics of public health intervention; however, there is no reason why intervention could not occur simultaneously with model validation.

The panel agreed that there was no easy answer to the validation question. Determination of whether results are accurate (validation) may not be possible due to the complexity of the exposure scenario and uncertainties regarding chemical behavior. As an alternative, a reasonableness standard might be substituted for an accuracy standard. Thus, an independent validator could determine whether the results are reasonable or plausible when considered in the context of the current state of knowledge. Validation could be partial, on different components. Sensitivity analysis would be useful to focus validation efforts. Try models built from different perspectives. Construct them differently and compare the different models to see if they come out differently.

Seveso was cited as an example that could be used for validation, since it was an acute episode of exposure, followed over time. Chronic events are more unusual. Apply the model to those situations.

Investigations of DBPs might be an example. Looking at the outcome and measuring some compounds might help with a partial validation. Verification is more reasonable than validation because one can go from one to another. First it is important to show that the model can work. Depending on the outcome of the model, follow up in the form of data collection, model modification, or calibration may be necessary. After that depends on how the initial results look.

Evaluating up to a biomonitoring level, by predicting movement of a chemical from a source to a tissue measurement, is doable. Going to a health endpoint is harder, although it has been done in simple situations.

EPA could open this issue up to the broader risk assessment community by conducting a workshop at the Society for Risk Analysis (SRA) or a similar meeting and engaging attendees in interactive simulation with the method.

What would be the best ways to publish and present the information in Chapters 1 through 6 so that it would be of most use to the intended users, e.g. risk assessors, risk managers and decision makers concerned with CRA?

What would be the best ways to publish and present the information in the Glossary (Chapter 7) and Appendices so that it would be of most use to the intended users, e.g. risk assessors, risk managers and decision makers concerned with CRA?

It is essential that the full Approaches Document be available from some source, together with the appendices and glossary. The most obvious place would be the EPA Web site. An alternative would be EPA's Risk Assessment Forum.

However, the Approaches Document is a relatively technical one, and a great percentage of those people who are not personally engaged in risk assessment will not find it on the EPA Web site, and even if they were to find it, they would not invest the time and energy to try to understand it. Therefore, it is essential that the information presented in the document be available in other sources. Ideally, this should be reports in peer-reviewed journals, directed at the various communities that would be interested in the document. Every effort should be used to (1) identify the different scientific communities that should see the information, (2) identify the

journals that the different scientists read, and (3) prepare for submission to at least one journal that would reach each of the identified scientific communities.

Examples of these different scientific groups are as follows:

- *The risk assessment community*. This community will undoubtedly find out about the Approaches Document, and will probably want to review the entire document. Therefore, having the full document available from some source like the EPA Web site, will be important. It would also be beneficial to have a technical publication that summarizes the approach in a journal such as *Risk Analysis*.

- *The environmental health community*. This community reads journals such as *Environmental Health Perspectives, Environmental Research*, and *Environmental Science and Technology*. The most visible of these journals is *Environmental Health Perspectives,* which would be an ideal place for a publication, preferably as a full report. Alternatively, it could be submitted as a commentary, which is in general a shorter and less technical report. Another possibility (preferably in addition to a paper in *Environmental Health Perspectives*) would be a longer review of the CRA process for a journal such as *Reviews in Environmental Health*. While this would not reach as large an audience, it would allow a much more detailed presentation of the information in Chapters 1–5, although still something much shorter than the full document.

- *The public health community*. The public health community overlaps a bit with the environmental health community, but reads quite different journals. The best access to this community is through the *American Journal of Public Health.* Articles submitted to this journal tend to be much less technical in nature than those for *Environmental Health Perspectives* or other environmental health journals. However, this journal is read by a very large community of individuals in local, country, state, and federal public health agencies, and this community will be most focused on socio-economic and cultural factors related to risk.

- *The regulatory and industrial community*. This community reads *Regulatory Toxicology and Pharmacology*. This is a very important community that should know the results of these considerations, as already indicated by the nature of public comments received from several companies and organizations.

- *Symposia and conferences*. Every effort should be made to present the results reported in the Approaches Document at conferences and symposia. This will have the benefit of a meeting, yet with different audiences, stimulating discussion among interested groups, including students, and providing feedback to the authors in the form of questions and suggestions.

Fix the definition of pharmacokinetics (reference should be to toxicokinetics, not toxicodynamics) in Chapter 7.

9.0 References

Bradford Hill A. 1965. The environment and disease: association or causation? Proc Royal Soc Med. 58:295-300.

Chrostowski PC. 1994. Exposure Assessment Principles. Chapter 8 in Patrick DR (ed). Toxic Air Pollution Handbook. VNR New York.

Dennison JE, Andersen ME, Yang RS. Characterization of the pharmacokinetics of gasoline using PBPK modeling with a complex mixtures chemical lumping approach. Inhal Toxicol. 2003 September 15(10):961-86.

EPA. 1997. Guidance on Cumulative Risk Assessment, Part 1. Planning and Scoping. Science Policy Council, Washington, DC. Attachment to memo dated July 3, 1997 from the Administrator, Carol Browner, and Deputy Administrator, Fred Hansen, titled Cumulative Risk Assessment Guidance-Phase I Planning and Scoping. Available at http://www.epa.gov/OSA/spc/2cumrisk.htm.

EPA. 2000. Supplementary Guidance for Conducting Health Risk Assessments of Chemical Mixtures. Risk Assessment Forum, Washington, DC. EPA/630/R-00/002. August 2000.

EPA. 2001. Risk Assessment Guidance for Superfund Volume 3 Part A: Process for Conducting Probabilistic Risk Assessment. Office of Emergency and Remedial Response, Washington, DC. EPA 540-R-02-002. December 2001. Available at http://www.epa.gov/oswer/riskassessment/rags3adt/index.htm.

EPA. 2002. Lessons Learned on Planning and Scoping of Environmental Risk Assessment. Memorandum from Science Policy Council. January. Available at http://www.epa.gov/osp/spc/llmemo.htm.

EPA. 2003. Framework for Cumulative Risk Assessment. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/600/P-02/001F. Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944.

EPA. 2005. Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities, Final. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response (5305W), Washington, DC. EPA/520/R-05/006. Available at http://www.epa.gov/epaoswer/hazwaste/combust/risk.htm.

EPA. 2006. Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects (External Review Draft). National Center for Environmental Assessment, Office of Research and Development. EPA/600/R-06/013A. March 2006.

Gierthy JF, Arcaro KF, Floyd M. 1997. Assessment of PCB estrogenicity in a human breast cancer cell line. Chemosphere 34:1495-1505.

Guzelian PS et al. 2005. Evidence-based toxicology: a comprehensive framework for causation. Hum Expt Toxicol 24:161-201.

Haddad S, Beliveau M, Tardif R and Krishnan K. 2001. A PBPK model-based approach for the risk assessment of chemical mixtures. Toxicological Sciences 63: 125-135.

Howard. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Lewis Publishers.

Mackay et al. Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals. Lewis Publishers.

(NRC) National Research Council. 2004. Review of the Army's Technical Guides on Assessing and Managing Chemical Hazards to Deployed Personnel. A report by the Subcommittee on the Toxicological Risks to Deployed Military Personnel, Committee on Toxcicology. National Academy Press, Washington, DC.

Nong A and Krishnan K. 2005. Route to route extrapolation of metabolic interactions among alkylbenzenes in humans: use of a physiological modeling approach. In: JG Anderson and M Katzper (Eds.), Proceedings of the 2005 International Health Sciences Simulation Conference (ISBN 1-56555-289-X). The Society for Computer Simulation International, San Diego, pp 111-116.

Susser M. 1991. What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am J Epid 133:635-48.

Appendix A. List of Peer Reviewers

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External Peer Review Panel Meeting for "Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects"

U.S. EPA / NCEA
Cincinnati, Ohio
May 25–26, 2006

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Note: Dr. Carlisle is participating in this review as an independent expert, and not as a representative of OEHHA, Cal EPA.

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Appendix B. Charge to Reviewers

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External Peer Review Panel Meeting for
"Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects"
May 25–26, 2006

Charge Questions Organized by Chapter

Chapter 1

1a. Comment on the level of detail in the Chapter, specifically on its adequacy in citing and explaining currently available methods and guidance for assessing multiple chemicals, exposures and effects. What other relevant guidance related to exposure and toxicity combinations needs to be cited? Provide citations for any other significant materials or reports that need to be included in the document.
1b. Comment on the adequacy of the Chapter to set the stage for subsequent discussions of expanded and new approaches in Chapters 3 through 5.
1c. Comment on the scientific rigor of the information presented in the Chapter, specifically discussing the logic and description of the cumulative risk approach.

Chapter 2

2a. Comment on the level of detail in the Chapter, specifically on its adequacy in citing and explaining currently available methods and guidance for assessing multiple chemicals, exposures and effects. What other relevant guidance related to exposure and toxicity combinations needs to be cited? Provide citations for any other significant materials or reports that need to be included in the document.
2b. Comment on the adequacy of the Chapter to set the stage for subsequent discussions of expanded and new approaches in Chapters 3 through 5.
2c. Comment on the scientific rigor of the information presented in the Chapter, specifically discussing the logic and description of the cumulative risk approach.

Chapter 3

3a. Comment on the logic and scientific rigor of the information presented in the Chapter.
3b. Comment on the usefulness of these approaches to risk assessors who are interested in assessing multiple chemicals, exposures and effects.
3c. Based on your knowledge of the field, describe the extent to which the methods are new and innovative or, conversely, commonly known to risk practitioners. In your response, consider the combining of existing models or methods as an area of innovation. Note other methods, data or citations in the open literature that should be added.

Chapter 4

4a. Comment on the logic and scientific rigor of the information presented in the Chapter.
4b. Comment on the usefulness of these approaches to risk assessors who are interested in assessing multiple chemicals, exposures and effects.
4c. Based on your knowledge of the field, describe the extent to which the methods are new and innovative or, conversely, commonly known to risk practitioners. In your response, consider the combining of existing models or methods as an area of innovation. Note other methods, data or citations in the open literature that should be added.

4d. The document proposes to group chemicals by co-exposures and common effects for analysis using chemical mixtures risk assessment methods. Considering chapters 3 and 4:
   i. Describe the usefulness of this approach to handling multiple chemicals, exposures, and effects.
   ii. Discuss the logic and transparency of the approach, highlighting any inconsistencies or needed improvements in the approach.
   iii. Once the chemicals are grouped, comment on the clarity of the procedure regarding next steps, i.e., the application of chemical mixtures risk assessment methods for dose-response and risk characterization.

4e. The document emphasizes the need for cooperation and iteration between the exposure and toxicity assessment processes. Comment on the scientific basis for cooperation and iteration between exposure and toxicity assessments, providing your opinion on the need for this concept to be emphasized in the document.

Chapter 5

5a. Comment on the logic and scientific rigor of the information presented in Chapter 5.

5b. Comment on the usefulness of these approaches to risk assessors who are interested in assessing multiple chemicals, exposures and effects.

5c. Based on your knowledge of the field, describe the extent to which the methods are new and innovative or, conversely, commonly known to risk practitioners. In your response, consider the combining of existing models or methods as an area of innovation. Note other methods, data or citations in the open literature that should be added.

5d. Use of the compound and sophisticated models in this document introduces a great deal of uncertainty into the cumulative risk estimates. Does the document clearly delineate the sources of uncertainty introduced by this approach? Please provide guidance for developing a more comprehensive approach to characterizing the results of such models to address the many sources of uncertainty.

5e. Are the cumulative risk approaches in the document appropriate for addressing all types of health effects (e.g., cancer, neurological, behavioral, respiratory, etc.)? Which types of health effects are best addressed by them?

Overarching Issues/Questions

6a. What is the reviewer's overall evaluation of the scientific content, readability and utility of the entire document? Provide any suggestions relative to structure or content that would improve the quality of the document.

6b. In general, comment on how well the text in the document supports the ideas shown in the Figures. How should the examples be modified to adequately illustrate the concepts?

6c. In general, comment on the consistency of the suggested approaches with current Agency guidance from a technical perspective. How, if any, does the population focus alter any existing technical procedures or assessment steps, including information requirements? Which existing EPA procedures or methods would be affected and in what manner? Specify any better examples and data tables that could be used to demonstrate feasibility of assessing multiple chemicals, exposures and effects.

6d. It is acknowledged in this document that employing worst-case assumptions for all pathways of exposure and health endpoints is unreasonable. What advice would you provide to EPA regarding a balanced approach for choosing assumptions for these cumulative risk models?

6e. To what extent does this document provide useful and practical information and advice

for risk assessors who are faced with real world situations?

6f. Is the approach proposed likely to lead to realistic risk scenarios? What validation exercises would you suggest for the risk assessor? How might EPA demonstrate such a validation approach? Are their places in the document where real-world examples may provide utility? Can you suggest any desk-top exercises that might be used to evaluate the utility of the approaches described in this document?

6g. What would be the best ways to publish and present the information in Chapters 1 through 6 so that it would be of most use to the intended users, e.g. risk assessors, risk managers and decision makers concerned with cumulative risk assessment?

6h. What would be the best ways to publish and present the information in the Glossary (Chapter 7) and Appendices so that it would be of most use to the intended users, e.g. risk assessors, risk managers and decision makers concerned with cumulative risk assessment?

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Appendix C. Pre-Meeting Issues Identified by Peer Reviewers

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Jim Carlisle

1. General – Overall, this document is thorough and well written. The chapters are well integrated with some overlap. Despite its nearly 300 pages, it contains little that is truly new; it is more of a re-combination of pre-existing concepts and methods. Presumably, that was the Agency's intent.

2. Dose-Response Analysis (pertains to question 5)
   The idea of changing dose-response analysis so that it occurs concurrently and iteratively with exposure assessment, while scientifically sound, will have major implications for the way EPA (and other organizations) do business. Such a major structural change needs careful thought and consideration of all the implications. Currently, dose-response analysis typically occurs independently of site investigation and analysis. It is typically done in a highly controlled and structured manner, with input and peer review from many sources. For example the health criteria in the IRIS database criteria undergo extensive review before becoming final. To do this on a case-by-case basis would be exceedingly resource intensive. It is difficult to imagine that the same level of review and scientific consensus-building would go into a site-specific analysis.
   A possible alternative to concurrent dose-response analysis is to employ "look-up" criteria as we have now, but to generate criteria for more time points such as acute, subacute, and subchronic. Even this scaled-down approach will require a major effort to "mine" existing data or generate new data to develop a time-dependent toxicity database to be used in conjunction with time-dependent exposure information. Most long-term toxicity studies have only a terminal sacrifice or at most that plus one interim sacrifice. Data recorded on a more frequent basis are limited. Thus, for many chemicals, time-to-effect data will be difficult to come by unless new studies are completed. Even if we were to make the financial commitment to this daunting task, it would take decades to accomplish.

3. Definition of "Response Additivity" - The concept of response additivity makes sense for carcinogens that are assumed to exhibit a linear relationship between dose and cancer risk because the cancer risk is expressed as a probability and probabilities for independent events are additive. But for toxicants that act by a mechanism that exhibits a toxicologic threshold, response additivity does not seem to be an appropriate way to characterize the relationship between the effects of two toxicants, since there are no probabilities to add. Imagine the following scenario:

   A person is simultaneously exposed to both toxicant A and toxicant B, each at a dosage that results in a HQ of 0.6. If the two toxicants affect a common target organ or act by a common mechanism (e.g. they both inhibit cholinesterase), we would use the dose additivity paradigm, and the resulting HQ of 1.2 would lead us to conclude that the exposed person may experience the combined toxic effects of the 2 toxicants. However, if the two toxicants act by separate and independent mechanism and do not affect the same target organ, we would not add the two separate HQs of 0.6 and we would presume that the exposed person would not experience the toxic effects of either toxicant, since each exposure would be below the threshold for that toxic effect. Response additivity does not make sense for threshold toxicants.

4. Definition of "Antagonism" – Antagonism should be defined as an interaction in which the presence of a second chemical reduces the toxicity of the first. Casarett and Doull

define antagonism as “the situation in which two chemicals, administered together, interfere with each other’s actions or one interferes with the action of the other chemical”. This situation is very different from that in which simultaneous exposure to two chemicals result in less than additivity because they do not share a common target organ or mechanism of toxic action, and neither has any effect on the toxicity of the other. The latter situation deserves a separate term like “independence” or “non-additivity”. While both situations would clearly result in less than additivity, they are conceptually very different and should not be lumped together.

5. Definition of “Interactive” - According to text box 1-2, chemicals that are not additive because their modes of toxicological action have nothing in common and their target organs are completely different are defined as interactive. On the other hand, two chemicals that act in an additive manner because they affect the same target organ or biochemical pathway are defined as non-interactive. This is completely backward. The term “interactive” should be reserved for combinations of chemicals that interact in some manner, be it additive, synergistic, or antagonistic. It should not include combinations of chemicals that act independently.
   Casarett and Doull include additivity (along with synergism and antagonism) under the heading “Interaction of chemicals”, stating: “A number of terms have been used to describe pharmacologic and toxicologic interactions. An additive effect is the situation in which the combined effect of two chemicals is equal to the sum of the effect of each agent given alone.”

   The definition of “Interaction” in text box 1-2 is an unfortunate, misleading, and counterintuitive one that describes what is essentially “any situation other than straight additivity”. Adoption of the proposed usage would result in the absurd situation wherein chemicals that act in a non-additive manner because they have no commonality of target organ or mode of action are defined as interactive, while chemicals that interact in an additive manner because they have a common target organ or mode of action are defined as non-interactive. This is not only contrary to what one would assume based on an ordinary dictionary definition, but it is also conceptually flawed. I can agree with the definition in the glossary, except for the last sentence. Interestingly, the definitions of “no observed interaction” and “toxicologic interaction class” appear to be correct.

David Carpenter

1. While recognizing that this may be too much for this particular committee to handle I have an issue that is critical to any risk assessment, which is that I believe that the fundamental assumptions behind the RfD are flawed. The assumption is that there is a threshold for all non-cancer effects below which there is no harmful effect to humans, stated very clearly on page 41 of the Supplemental Guidance document. I don't believe this to be true, nor do I know of any evidence that it is true. In one specific area of concern in which I am very involved, that being neurobehavioral effects of substances such as lead, PCBs and environmental tobacco smoke on IQ of children, there is clear evidence that this assumption does not hold. For each there is increasingly clear evidence that there is no threshold, and in fact for both lead and environmental tobacco smoke there is evidence that the incremental IQ decrement at concentrations previously thought to be without effect is greater than what is found at higher concentrations. In many other areas there are observations of low dose effects occurring below the RfDs and demonstrations of non-linear dose-response relationships. So there are two questions: is the concept of the RfD appropriate, or is it only that we do not always have adequate information on which to determine a NOAEL. I suspect the former is the true case. While a total restructuring of the ways in which EPA does risk assessment is not something I am calling for, I would like this problem to be considered in the context of the documents under review. This issue runs throughout the document, but is first introduced in the context of mixtures on 1-13.

2. Another less global issue related to assumptions made by federal agencies is that of effects of volatile solvents and semi-volatile compounds. This is discussed on 2-14 in relation to ATSDR, which makes the assumption of effects only close to the source. Again, drawing from my personal studies, I find this assumption to be wrong. Hermanson et al. (ES&T 37: 4038-4042: 2003) has shown elevated PCB levels (a compound not usually even acknowledged to be volatile) in tree bark up to three miles from contaminated sites. Our studies have shown elevated incidence of hospitalization for several chronic diseases (myocardial infarction, stroke, hypertension, chronic bronchitis) among individuals living near to hazardous waste sites contaminated with persistent organic pollutants(near defined by zip code of residence, obviously a crude index of exposure). These relationships stand after control for SES, smoking, diet and exercise patterns, and appear to be exposure dependent. This issue is relevant to this document only in so far as to point to the dangers of accepting assumptions, and the fact that as discussed on 3-49 models often "winnow down the list of chemicals of concern and exposure pathways by eliminating those clearly not expected to contribute to adverse effects". Thus the assumptions made are critical to an appropriate risk assessment.

3. It is totally inappropriate to focus on "pregnant women" (as is done in 3-10 and 5-4) for protection of neurobehavioral toxicants. If you wait until pregnancy it is much too late to prevent harmful effects from many chemicals, since the half life of organochlorines like PCBs is of the order of 10 years and even methyl mercury is 70 days. Risk assessment for very persistent compounds should focus on females from birth to menopause for protection of the infant, and for more limited periods for others, but always not waiting until pregnancy.

4. There is a level of complications concerning contaminant metabolites that is not considered, that being when a metabolite has a different and sometimes even an opposite action from the parent (4-12). This is the case for some parent PCB congeners and their metabolites, in that the parent may be antiestrogenic but the metabolite estrogenic (Gierthy et al., Chemosphere 34: 1495-1505: 1997). This problems complicates the RPF approach (5-11), although the problem is certainly acknowledged. But as we learn more about mixtures even of chemicals of the same general class (PBDEs, dioxins/furans, PCBs, toxaphene) we find that each congener has its own profile of biological actions, and often two congeners of the same class can have totally different and even opposing actions. This problem is also relevant to the discussion of the CHI (5-15/16).

5. There needs to be greater consideration of actions of chemicals and mixtures that are indirect (4-16). For example dioxins stimulate enlarged livers, and the livers then may do a variety of things that have nothing to do with the induction of P450s, such as cause elevations in fasting glucose levels or increase the synthesis of cholesterol and other lipids. Often these effects are not appreciated even as possibilities until demonstrated in animals or people.

Paul Chrostowski

General Comments

1. The document could use an example that is carried all the way through the process. There are some good partial examples in the different chapters; however, I think it would help to clarify the process if the examples were carried all the way through. For example, Figures 4-8 and 4-9 present elements of a moderately complex risk assessment that could be used as the basis of a continuing example through the risk characterization process.

2. When it comes to dose-addition or response addition, a problem seems to arise when dealing with mixtures of chemicals that have RfDs (or CSFs) and chemicals that are assessed by other means. For example, lead is usually assessed by biokinetic modeling, Clean Air Act criteria pollutants are usually assessed by comparison to an air quality standard and most other hazardous substances are assessed by means of RfDs. These dose-response metrics are not equivalent, however, some method needs to be developed to handle them additively. A similar issue could relate to mixtures of carcinogens where individual components are assessed by Margin of Exposure or stochastic approaches.

3. Tables 3-1and 3-5 contain a substantial amount of information on environmental fate and transport, however, it is unclear how this information is to be used. Is EPA espousing these values as definitive or defaults? There is a substantial literature regarding values such as these, for example, Mackay et al's 5-volume series *Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals* (Lewis Publishers), Howard's 5-volume *Handbook of Environmental Fate and Exposure Data for Organic Chemicals* (Lewis Publishers), etc that present numerous values for fate and transport parameters that may or may not correspond to the values in Table 3-1. How should the Table 3-1 values be viewed in light of the literature. Additionally, many of the entries on the table are incomplete or site-specific. Some are implausible such as a single value Kow for "PCBs". As an of incomplete and site-specific information, DDD and DDE are only two of over a dozen metabolites of DDT and may be insignificant metabolites in some situations. The concept of half-life has only limited applicability in the natural environment and its use should be highly qualified.

4. The concept of a health endpoint as the trigger is a great concept. Very often EPA or a private party must respond to complaints of health effects from the community which wants to know if there is a link between chemical exposure and a health effect. Oftentimes these complaints are addressed by a health study or a mini-epidemiologic study. If health is the endpoint that triggers the risk assessment, there needs to be some way of associating the risk characterization results to the endpoint. For example, how will the risk assessment be used to investigate a leukemia cancer cluster in a community? Will individual exposure factors be used? Will EPA be able to develop MLE (or age-, gender-specific) cancer slope factors?

5. A health-driven risk assessment also needs to deal with the concept of causation. EPA decisions regarding hazard identification are based on weight of evidence concepts rather than causation concepts. Community members will want to know if the emissions from the factory are causing the leukemia cancer cluster, not the upper bound probability of a hypothetical person contracting some kind of cancer. EPA might want to consider

integrating concepts from classical causation (e.g. Bradford Hill[1], Susser[2]) or evidence-based toxicology[3] to make risk assessment results more realistic.

More focused comments

6. How will doses to target tissue arrived at through pharmacokinetic modeling be used in light of the fact that most EPA dose-response data is based on administered dose rather than dose at the target tissue?

7. EPA has derived toxicological data for only a small group of chemicals compared to the larger universe that people might be exposed to. How will toxicological data gaps be handled in the cumulative risk assessment?

8. A more concrete way of limiting the number of chemicals in an assessment is needed. Perhaps screening algorithms based on toxicity, bioaccumulation, and persistence parameters should be used.

9. Severity (e.g. p. 4-35, 4-36) was previously used in the derivation of Superfund reportable quantities. How do these two methods compare?

10. The categorical regression method (page 4-34) is intuitively more satisfying than an RfD approach, however, it is data intensive and may not be feasibly for many common toxicants. An example would also be helpful here.

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1 Bradford Hill, A. 1965. The environment and disease: association or causation? Proc Royal Soc Med. 58:295-300.
2 Susser, M. 1991. What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am J Epid 133:635-48.
3 Guzelian, P.S. et al. 2005. Evidence-based toxicology: a comprehensive framework for causation. Hum Expt Toxicol 24:161-201.

Kannan Krishnan

Issues for discussion

- How about probabilistic non-cancer risk assessment for mixtures

- In multi-route assessments, is the reference dose considered the same (regardless of the route of exposure), particularly if the critical effect is route-independent (the case of systemic toxicants)

- The computation of HI on the basis of internal doses: does it relate to target organ toxicity dose (TTD) or to a measure of tissue exposure simulated with PK models

- The use of PBPK modeling in mixture risk assessment has not been developed as well (there are published examples of cancer and non-cancer assessment based on the consideration of the extent of interactions simulated with PBPK models).

Nga Tran

Draft Issues

Chapter 1:

Health endpoint (population illness) as the trigger for cumulative risk assessment: health effects have multiple risk factors and the process of attributing risks is often complex. The process of identifying chemicals relating to the health endpoint trigger needs to be discussed in context of this multi-factorial risk perspective. The CRA framework, as laid out in this document, is driven by source/chemical groupings, at least as a starting point, and much of the cumulative concepts are screening level assessments. Therefore, it is unclear, what options are being suggested when health endpoints are triggers.

Chapter 2:

Preliminary characterization of the population is based on the trigger of the CRA. Among the triggers discussed is environmental concentration. Biomonitoring data are also possible triggers and should be discussed.

Linking the list of chemicals of concern to the population profile through a conceptual model (page 2-21, line 8) – an influence diagram was mentioned but it's not clear what diagram it is referring to.

Chapter 3:

The chapter indicated that the main emphasis for cumulative assessment is on how sources, chemicals, media and receptors can be grouped for joint pathway analysis:

- Potential for co-occurrence in each compartment/medium
- Potential for interactions affecting transformation
- Potential for co-occurrence and interaction among each transport pathway between media

If the purpose of these grouping is to generate list of chemicals in each environmental compartment and at various time frames, then it needs to be stated more clearly.

Exposure quantification (3.3.3)

Past exposures are typically involved when a health endpoint has a lag time between exposure and outcomes, such as cancer. When these endpoint are triggers for CRA, cumulative dose reconstruction would be needed. Methods to assess past cumulative exposure should be included.

The discussion in this section ranged from screening to narrow down the list of CoC and to rank mixtures to very refined calendar and calendar-PBPK approaches. There are a number of issues in terms of data need and data quality as one proceeds from screening to more refined models. These issues need to be presented. Also, a more focused discussion of the levels of sophistication of the exposure assessments for CRA, i.e. screening approach (fate/transport grouping), measured vs. model concentration, body burden data, etc., and indication of when and

they are not applicable, would be helpful. Methods and options for probabilistic cumulative exposure assessment should also be added.

Chapter 4: Cumulative toxicity assessment

Chemical mixture grouping and toxicity assessment scheme: level of aggregation and resulting uncertainty about grouping methods should be discussed. For example, grouping based on common mode of action would be less uncertain than grouping based on common endpoints. Grouping based on SAR as an initial screening approach may also be suggested.

Chapter 5: Cumulative risk characterization

Trigger factor should be a prominent part of the final risk characterization (indicated in chapters 1 and 2). This was not addressed in the risk characterization chapter. A discussion of how the results of a CRA could be used is needed. Further, it would be extremely helpful to provide a summary of the types of CRA (from screening to refined/probabilistic approaches) that would be more appropriate for what triggers (health clusters, chemicals, or sources) and purposes (e.g. predict future or current risks, identification of intervention strategy, regulatory decisions, or determining exposure-effect association).

Feasibility and data quality: Quality data input are important consideration, especially when complex calendar models are used. A discussion on data quality and their appropriateness for the various CRA options would be helpful.

Cumulative HI: Impact of uncertainty factors when RfDs are used need to be further examined. The UFs are not explicitly addressed under this approach. On the other hand when aggregating MOEs (approach used under FQPA), UF are explicit in the scaling of MOEs for addition.

Ordinal regression calculation for multiple effects and pathways: The discussion to dismiss approach to address multiple effects of concern due to difficulties to incorporate into a risk management evaluation (partly due to the different effects would have to be ranked in order of public health concern, page 5-17) is too limited. There are available and neutral methods to rank order public health impacts for risk management evaluation, such as converting health impacts into disability adjusted life years (DALY). Options to expand the results of CRA to rank public health impacts explicitly should be provided.

Ordinal regression for multiple health effects is a reasonable expedited option to address multiple effects; however, grouping of endpoints by level of severity involves judgment and needs to be explicit. The document should also address the degree of aggregation and interpretation of results, i.e. screening estimates only?

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Appendix D. List of Registered Observers

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External Peer Review Panel Meeting for "Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects"

U.S. EPA/NCEA
Cincinnati, Ohio
May 25–26, 2006

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Appendix E. Agenda

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External Peer Review Panel Meeting for "Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects"

U.S. EPA/NCEA
Cincinnati, Ohio
May 25–26, 2006

Agenda

THURSDAY, MAY 25, 2006

9:00 am	Welcome, Meeting Purpose, and Introductions ..... *Jan Connery, Meeting Facilitator ERG*
9:15 am	Background ..... *Linda Teuschler National Center for Environmental Assessment (NCEA) U.S. Environmental Protection Agency (EPA)*
9:30 am	Public Comment ..... *Jan Connery*
10:00 am	Review of Charge and General Impressions ..... *Kannan Krishnan, Panel Chair University of Montreal*
10:15 am	Chapter 1. Introduction to Cumulative Risk at the U.S. EPA *Lead Discussant: James Carlisle, California Environmental Protection Agency*
10:45 am	BREAK
11:00 am	Chapter 2. Initial Characterization of the Population and Chemicals of Concern *Lead Discussant: David Carpenter, University of Albany, Institute for Health and the Environment*
11:30 am	Chapter 3. Cumulative Exposure Assessment *Lead Discussant: Paul Chrostowski, CPF Associates, Inc.*
12:30 pm	LUNCH
1:30 pm	Chapter 3. Cumulative Exposure Assessment (continued) *Lead Discussant: Paul Chrostowski*
2:45 pm	Chapter 4. Cumulative Toxicity Assessment *Lead Discussant: Kannan Krishnan*
3:30 pm	BREAK

3:45 pm Chapter 4. Cumulative Toxicity Assessment (continued)
Lead Discussant: Kannan Krishnan

5:30 pm ADJOURN

FRIDAY, MAY 26, 2006

8:00 am Discussion of Outstanding Issues from Day 1 ..... *Kannan Krishnan, Panel Chair*

9:00 am Chapter 5: Cumulative Risk Characterization
Lead Discussant: Nga Tran, Exponent, Inc

10:15 am BREAK

10:30 am General Charge Questions
Lead Discussant: Kannan Krishnan

11:30 am Writing Session (Includes Working Lunch)

1:00 pm Development of Conclusions and Recommendations

2:55 pm Closing Remarks

3:00 pm ADJOURN

Appendix F. Slides of the Presentation by Linda Teuschler, EPA

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Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects External Review Draft (2006)

Introductory Talk

Linda K. Teuschler

Scientific Peer Review Meeting

May 25-26, 2006

Cincinnati, Ohio

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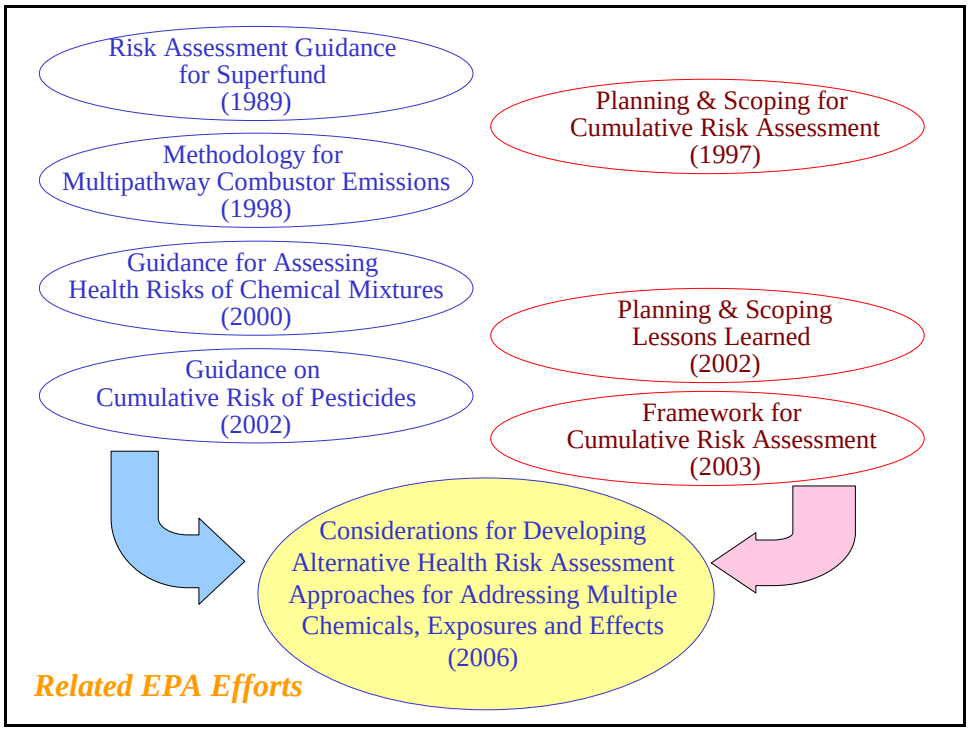


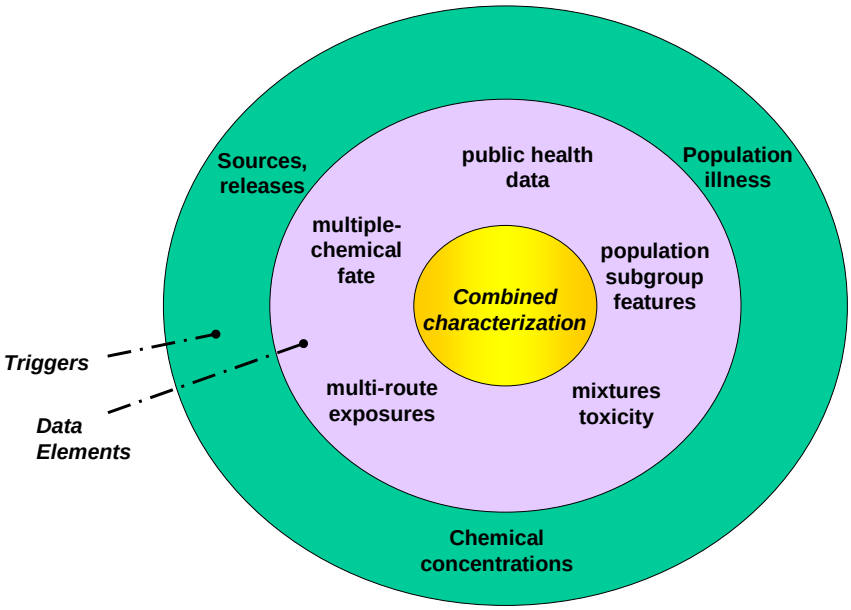
Definitions from EPA's 2003 Framework for Cumulative Risk Assessment (EPA/630/P-02/001F)

- Cumulative Risk: The combined risks from aggregate exposures to multiple agents or stressors.
- Agents or Stressors: May be chemicals, biological or physical agents, or the absence of a necessity such as habitat.
- Cumulative Risk Assessment: An analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors.

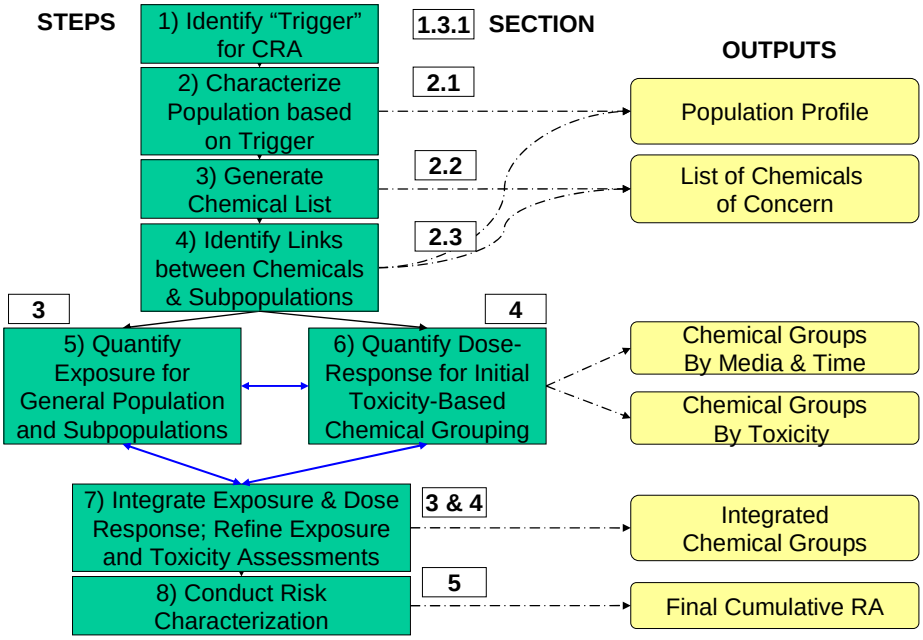
Focus of this 2006 "Approaches" Document (EPA/600/R-06/013A)

- Concepts and methods for potential use in the conduct of cumulative risk assessments (This is NOT a regulatory document and is NOT official EPA guidance.)
- Combined human health risks for aggregate exposures to multiple chemicals (Does not address biological or physical stressors.)
- Exposure methods consider multiple pathways, routes, environmental transformations, timeframes.
- Toxicity methods consider multiple effects, toxicological interactions.
- Identify existing risk assessment guidance, data and risk information for use in assessing multiple exposures, effects and chemicals

Information Gathering & Processing



Key Steps in a Cumulative Risk Assessment



New & Emerging Approaches

- Grouping chemicals for risk assessment based on exposure characteristics and toxic endpoints
- Multiple route combinations of Relative Potency Factors
- Internal doses to account for multiple route exposures
- Integration of categorical regression multiple effects modeling with additivity methods
- Interaction-Based Hazard Index
- Emphasis on interdependence of toxicity and exposure for assessing risk
- Considerations for cumulative risk characterization, using Cumulative Hazard Index as an example
- Cumulative Risk Toolbox (Appendix A) of existing information for use in assessing multiple exposures, effects and chemicals

Document Organization: Chapters & Appendices

1 Introduction to Cumulative Risk at the U.S. EPA
2 Initial Characterization of the Population and Chemicals of Concern
3 Cumulative Exposure Assessment
4 Cumulative Toxicity Assessment
5 Cumulative Risk Characterization
6 References
7 Glossary

Appendix A: Cumulative Risk Toolbox

Appendix B: Toxicity Information to Support Groupings

History & Next Steps

- Feb 2001: NCEA began work developing cumulative risk approaches and information through an Interagency Agreement with the Department of Energy
- Nov. 2004: Superfund Program Office & Regional Internal EPA Review
- March 2006: External Review Draft released for a 45 Day Public Comment Period.
- May 2006: Scientific Peer Panel Review
- June 2006: Final Report from Peer Panel Review
- 2006: Final Draft to be published following changes made in response to internal EPA, public and panel comments.