Peer Review Summary Report

External Peer Review of EPA's *Guidelines for Human Exposure Assessment*

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EXECUTIVE SUMMARY

Versar, Inc. (Versar), a contractor for the Environmental Protection Agency (EPA), coordinated an external peer review of EPA's "Guidelines for Human Exposure Assessment", and organized a 1.5-day public peer review meeting in Arlington, Virginia on August 15 and 16, 2016. The peer review of EPA's document was initiated with a pre-meeting written peer review managed by Versar and conducted by nine independent expert peer reviewers. The role of the peer reviewers was to evaluate the scientific and technical merit of the EPA document and provide their responses to 10 charge questions. Peer reviewers were charged only with evaluating the quality of the science included in EPA's document and were not charged with reaching consensus in either their deliberations or written comments. The 1.5-day peer review meeting, which directly followed the written peer review period, was held to discuss the scientific basis supporting EPA document and to provide members of the public with an opportunity to observe the peer reviewer deliberations.

On the first day of the meeting, Versar began by providing information on the overall peer review process and introducing the peer reviewers. In addition, EPA provided background information on the draft document and approach used in the development of the document. An observer comment session followed the opening remarks by Versar and EPA, after which the peer reviewers began their discussion on the document. The discussion was moderated by the Chair, Dr. Clifford Weisel, and focused on individual responses to EPA's charge questions. The second day of the meeting began with brief remarks from Versar followed by a second observer comment session and then continued discussion of responses to the charge questions.

Important discussion points, generally agreed upon by all reviewers, are summarized in the list below.

- The document is logical and clearly written, and the reviewers appreciated the document as a rich source of information and references on all aspects of exposure assessment.

- A few reviewers thought the intended audience was unclear, in part because the level of detail varied too much throughout the document.

- Many terms in the document were not defined, not clearly defined, or not used in a consistent manner throughout the entire document. It was suggested that a glossary of important terms be included and cross-checked with how the terms are used in each chapter. Some terms specifically mentioned include: communication, stakeholder, community, internal dose, dose, agents, stressors, vulnerability, susceptibility, maximum exposure range, dose metric, exposure metric, exposure science, and microenvironment.

- The utility of the document would be improved by adding a key points section at the end of each chapter to highlight that chapter's major points.

- Although the document clearly states that it will focus on traditional exposure assessments, some reviewers felt that a short chapter or appendix on emerging technologies should be included.

- The document should include more concrete examples to illustrate the concepts being discussed, including real-world calculations and conceptual frameworks.
  - One reviewer suggested having an appendix with examples that covers multiple chapters.
  - Many reviewers thought the examples needed more details.
  - Some reviewers did not like the drum leakage example used to illustrate a conceptual model as it excludes many possible sources, pathways and routes of exposure. Three alternate examples of EPA conceptual models were provided by one reviewer.

- The reviewers suggested the following changes to the exposure equations as presented in the document:
  - Provide the full equations, rather than a simplified form, so that users will have a complete understanding of the equation.
  - Include the dermal permeability coefficient in the dermal exposure equation.
  - Include a time component or duration for comparison with toxicological benchmarks.
  - Emphasize the need to match exposure or dose metrics with toxicological benchmarks.

- The reviewers commended EPA on the addition of vulnerable groups in the guidelines, but discussed many areas of potential improvement for Chapter 4. Some examples are:
  - The distinction between vulnerability and susceptibility should be made clear and consistent throughout the document. Consider discussing how the concepts of vulnerability and susceptibility should be integrated into an exposure assessment separately in Chapter 8. Examples would be very helpful.
  - Expand the discussion about exposure to pregnant women, fetal and elderly populations.
  - To be congruent with population numbers, more emphasis should be placed on children (~125 million) than tribal members (~5.2 million), and more emphasis could be added to economically disadvantaged individuals, of which tribal members are often a part.
  - EPA should solicit input from tribes on the language, activities, and potential exposure sources used in the section on Native American tribes.
  - Emphasize in this and other chapters the importance of working with community to identify their concerns early in the process and to understand the culture and community. This information will be used to develop a valid risk assessment and risk management plan.

- The reviewers generally agreed that Chapter 6 does a good job explaining model selection. Some suggestions included:
  - Emphasize that a more complex model is not necessarily a better model.
  - Include a list of models.
  - Augment the geospatial model discussion.
  - Provide uniform level of details for each model.
  - Emphasize how modeling efforts and data collection can be used together.

- The discussion of corrections of biomarkers in body fluids should not be limited to creatinine in urine.

- The reviewers agreed that communication is a very important part of the document and a more cohesive presentation of the communication strategies should be included in each chapter and as a distinct chapter. Some suggestions included:
  - There was some confusion on how and why exposures were discussed in the absence of risk. A discussion and examples of communication strategies solely for exposure assessment and in context of risk should be provided.
  - The term "communication" needs to be defined and could be introduced in Chapter 3, where the benefits of developing a communication strategy early in the assessment should be emphasized.
  - The emphasis and title of Chapter 9 should be revisited and used to synthesize the discussion of when and how to communicate exposure with the public and communities.

- The document should emphasize that exposure assessment is on the same plane as the hazard assessment. If the exposure scenario and population parameters are not characterized properly prior to beginning a risk assessment the product is unlikely to be useful to the decision-maker. It is also required for risk management.

- It is important that all hyperlinks in the document work and that all models referenced are available on-line.

Some specific points emphasized, or additions suggested, by one or more reviewer include:

- Include a discussion on the determination of relative source contribution factors, such as discussed in EPA's *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health* (EPA-822-B-00-004), to ensure that aggregate exposure does not exceed health benchmarks.

- Emphasize multi-contaminant, multi-media, multi-pathway exposures throughout the document.

- Discuss how systematic review principles can be applied to the selection and evaluation of exposure information. It was suggested to include a list of potential resources to assist with literature searches, such as PubMed, Web of Science, HERO, and consumer product databases.

- Include a discussion on the importance of conducting a needs assessment and understanding the community's risk perceptions as an essential part of the problem formulation.

- The document implies that the Agency will have access to the raw data, which is not always the case (i.e., published literature). The document should include a discussion on how to handle situations when the Agency does not have access to the raw data.

- Include more information on biomonitoring data. In particular, add a discussion on combining biomonitoring data with environmental data to link sources and internal exposures and evaluating exposure/pharmacokinetic models.

- Include more information on indoor dust, and the connection between house dust and soil should be emphasized.

- Add specific advice on dealing with non-detect values, as well as choosing a method with a detection level that provides useful information relative to the toxicological benchmarks being used for the chemical(s) of interest.

- While the Agency generally deals with non-occupational settings, the document does not provide a convincing rationale for excluding occupational exposure assessment from most of the text (occupational exposure and occupational issues are included in several chapters such as Chapters 2-5 and 8).

- Include sources for model input parameters for critical parameters and a discussion that emphasizes the need for research to determine these parameters to reduce model uncertainty.

I. INTRODUCTION

I.1 Background on "Guidelines for Human Exposure Assessment"

The "Guidelines for Human Exposure Assessment" (U.S. EPA, 2016) provides an updated resource on assessing human exposure for exposure and risk assessors in the Agency, consultants, contractors or others who perform this type of work under Agency contract or sponsorship, as well as academic, industrial and others who perform this type of work in accordance with EPA policies and procedures. This document builds on and supersedes the 1992 "Guidelines for Exposure Assessment" (U.S. EPA 1992), incorporates advances in the field that have occurred since then, reflects current scientific practice across Agency programs and includes pertinent topics identified during public meetings and from a survey of the literature, including publications issued by the National Research Council of the National Academy of Sciences.

In the past 20 years there have been significant advances in technology used in exposure science and corresponding advances in exposure assessment methodologies. In addition, lessons learned over the past 20 years have led to changes in agency policies. Collectively, the development of new methods and changes in EPA policies necessitates that EPA significantly revise its exposure guidelines. EPA's Risk Assessment Forum (RAF) obtained broad participation in its efforts to update the 1992 document.

The "Guidelines for Human Exposure Assessment" is designed to aid exposure scientists in developing exposure and risk assessments, status and trends analyses, mitigation strategies, regulatory decisions and epidemiological studies. The update focuses on human exposure to chemical agents (stressors) and presents the general principles of exposure science (including assessment and monitoring). The exposed populations (e.g., receptors) to which this document refers are adults and children or other vulnerable groups within the human population. In addition, the focus of the work is on exposure assessment as currently practiced by programs at EPA. It does not, however, serve as a detailed instructional manual or supplant specific exposure guidance in use by Agency programs, nor does it endorse specific models or approaches that could have limited applicability or have become outdated. This document does not include detailed information on high-throughput exposure assessment, the implications of *in vitro* risk assessments on the field of exposure assessment or the ongoing ExpoCast program. As these emerging topics mature, the RAF will update this document.

The Guidelines has undergone internal (EPA-wide) and interagency review with revisions incorporated in response to comments received by reviewers.

I.2 Peer Review Process

On January 7, 2016, EPA announced in the Federal Register the release of the draft document *Guidelines for Human Exposure Assessment* for the purposes of public review and comment (https://federalregister.gov/a/2016-00077). Versar, Inc., an EPA contractor, was tasked with assembling nine scientific experts to evaluate the document, with expertise/experience in the following areas: (1) chemistry; (2) environmental engineering; (3) environmental health

sciences; (4) exposure science; (5) exposure assessment; (4) human subjects research (6) public health research (7) statistics and exposure modeling; and (8) life-stage susceptibilities.

The purpose of the peer review was to provide a documented, independent, and critical review of the document, and identify any necessary improvements to the documents prior to being published. In assembling these peer reviewers and coordinating the peer review, Versar was charged with evaluating the qualifications of peer review candidates, conducting a thorough conflict of interest (COI) screening process, independently selecting the peer reviewers, distributing review materials, maintaining contact with the peer reviewers, organizing and hosting the public peer review meeting, and developing a final peer review report.

Versar conducted an independent search for qualified scientific experts. In total, Versar evaluated 29 interested and available candidates. Versar considered and screened all 29 candidates against the selection criteria (1) having demonstrated expertise in the areas described above, based on information in their submitted resume, biographical sketch and/or current publications, (2) being free of any COI and the appearance of the lack of impartiality, and (3) being available to participate in-person in a 1.5-day peer review meeting in the Washington DC area in the summer 2016 timeframe. Once the evaluation process was completed, Versar selected the nine final peer reviewers. In addition, Versar selected Dr. Clifford Weisel as Chair of the peer review meeting due to his expertise in exposure assessment as well as his strong record of chairing and participating in peer review panels, scientific meetings, and workshops. A list of the final nine peer reviewers who participated in this review is provided below.

Following the selection process, Versar distributed EPA's draft document and 10 charge questions (see Section II) to the peer reviewers. The peer reviewers were asked to evaluate the scientific and technical merit of the draft document and provide their responses to the 10 charge questions. This included evaluating the appropriateness of the quality, accuracy, and relevance of the data in the documents. Peer reviewers were not charged with reaching consensus in either their written comments or public deliberations. In addition to being provided the draft documents and charge questions, comments submitted to EPA's public docket (Docket ID number EPA-HQ-ORD-2015-0684) during the document's 45-day public comment period were provided to the peer reviewers ahead of the meeting for their consideration. However, peer reviewers were not asked to evaluate or respond to comments submitted to the docket.

Versar managed the pre-meeting peer review period, which provided the peer reviewers approximately one month to evaluate the document and complete their written re views. Following receipt of the peer reviewers' draft comments, Versar compiled the comments into a pre-meeting peer review report and distributed them to the peer reviewers and EPA to prepare for the public peer review meeting. These preliminary responses to the charge questions formed the basis of reviewer discussions on Days 1 and 2 of the public meeting.

PEER REVIEWERS

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I.3 Peer Review Meeting

On August 15 and 16, 2016, Versar convened a public peer review meeting in Arlington, Virginia. This meeting was held to discuss the scientific basis supporting EPA's "Guidelines for Human Exposure Assessment" and to provide members of the public with an opportunity to observe the peer reviewer deliberations. The meeting followed the document public comment period, during which members of the public were able to submit written comments, and the pre-meeting written peer review period, during which the nine selected peer reviewers evaluated the EPA document and provided preliminary comments in response to the charge questions.

Versar managed the pre-meeting registration period, which allowed members of the public to register to attend the meeting in person or remotely via teleconference and/or webinar. Members of the public were able to register by telephone, email, or U.S. mail. In advance of the meeting, Versar provided all registered attendees with pre-meeting handouts, which included the agenda and logistics information.

On the first day of the meeting, Versar began by providing information on the overall peer review process and introducing the peer reviewers. In addition, EPA provided background information on the draft document and approach used in the development of the document. An observer comment session followed the opening remarks by Versar and EPA, after which the peer reviewers began their discussion on the document. The discussion was moderated by the Chair, Dr. Clifford Weisel, and focused on individual responses to EPA's charge questions. The

second day of the meeting began with brief remarks from Versar followed by a second observer comment session and then continued discussion of responses to the charge questions.

Approximately 20 public observers attended the peer review meeting in person and approximately 37 observers attended the meeting via teleconference and/or webinar. Many observers attended both in-person and via teleconference and/or webinar, depending on the meeting day. Please see Appendix A for the meeting agenda and Appendix B for a list of public attendees.

Following the public peer review meeting, peer reviewers were given additional time to complete their individual written reviews. These final written comments are contained in Sections III, IV, and V of this report. Written peer review comments, as well as comments submitted to the EPA docket by members of the public, will be considered by EPA as it revises the draft exposure guidelines.

II. CHARGE TO REVIEWERS

Overview Comment

1. Please comment on the overall utility of the draft Guidelines for Human Exposure Assessment to exposure assessors conducting traditional exposure assessments.

Chapter 2. Principles of Exposure Science/Exposure Assessment - provides a review of exposure science concepts and principles, including approaches and tools, that can be considered when planning and conducting exposure assessments.

2. Please comment on the completeness of the discussion of exposure science and its application to exposure assessment.

Chapter 3. Planning and Scoping and Problem Formulation - describes a process for planning, scoping and problem formulation for an exposure assessment. It emphasizes the importance of: establishing goals and objectives; building an interdisciplinary team; developing a conceptual model; identifying assessment options, available resources and data needs; producing an overall assessment plan; engaging and involving appropriate stakeholders; engaging and involving the community; establishing data quality objectives; and the importance of peer review.

3. Please comment on the content, organization, and presentation of the planning and scoping and problem formulation chapter.

Chapter 4. Consideration of Lifestages, Vulnerable Groups and Populations of Concern in Exposure Assessments - discusses how lifestages, vulnerable groups and populations of concern could be at increased risk for adverse health effects from environmental contaminants due to disproportionate exposure or varied responses to exposure, or both. This chapter invokes existing Agency guidance, along with examples of case studies, to discuss where techniques and considerations associated with lifestages, vulnerable groups and populations of concern can be applied in exposure assessments.

4. Please comment on the content, organization, and presentation of the information on lifestages and populations of concern.

Chapter 5. Data for Exposure Assessment - discusses data used for exposure assessments, including determining what data are needed; whether data are currently available and the quality of the available data; and when data are not available, whether the data should be developed to meet the needs of the project. Guidance on the assessment of data uncertainty and variability is also presented in this chapter.

5. Please comment on this chapter's discussion of the selection, assessment, and use of data in exposure assessments.

Chapter 6. Computational Modeling for Exposure Assessment - highlights concepts in modeling, including the principles of the modeling process. It provides an overview of modeling

for exposure assessment, outlines the criteria for choosing appropriate models based on the goals and data quality objectives and describes how to evaluate a model that might be useful for an exposure assessment. Chapter 6 also includes information on modeling inventories and clearinghouses, and resources that support the use of models of various levels of complexity.

6. Please comment on the presentation of issues related to selection and use of exposure models.

Chapter 7. Planning and Implementing an Observational Human Exposure Measurement Study - provides details on planning an observational human exposure measurement study. These studies are used in parts of the Agency to quantify people's exposures to chemicals in their everyday environments during their routine activities. This chapter discusses the issues surrounding planning an observational human exposure measurement study, including budget and logistical planning, establishing a study design, planning and executing both a pilot study and full field study and the importance of peer review. It also addresses ethical considerations that exposure assessors need to consider when interacting with study participants and the community.

7. Please comment on the discussion of planning and implementing an observational human exposure measurement study.

Chapter 8. Uncertainty and Variability in Exposure Assessment - considers uncertainty and variability in exposure assessments, incorporating them into planning, scoping and problem formulation (Chapter 3) and data quality objectives (Chapter 5). This chapter highlights how these concepts are used in the application of models in an exposure assessment.

8. Does chapter 8 provide sufficient guidance on considering and communicating uncertainty and variability in exposure assessment? If not, what additional content should the chapter include?

Chapter 9. Presenting and Communicating Results - highlights communication, emphasizing the importance of identifying the intended audience, the types of communication products, communication strategies that might be appropriate for different exposure assessments and related ethical considerations.

9. Please comment on the discussion of communicating exposure and risks.

Additional Comments

10. The peer reviewers can provide any additional comments that they feel would benefit the draft document.

III. GENERAL IMPRESSIONS

Paloma Beamer, Ph.D.

My overall impression is that the updated "Guidelines for Human Exposure Assessment" is an extremely well written document that is well organized and clearly presented. In general, it is very comprehensive with many great additions that bring the "Guidelines" into the 21st century. With the exceptions noted below, the information is accurate and the document has remarkably few errors for a document of this size with so many authors and different components to keep track of.

The writers of this document have done an excellent job of providing guidance on such a complex topic. The document is very comprehensive as there is material pertinent for using existing data, conducting observational studies, and exposure modeling as well as how they can be used together. The document will also make risk assessors aware of the importance of conducting aggregate and cumulative exposure assessments as well as using the most updated "Exposure Factors Handbook." Furthermore, it is very important that this document contains chapters on vulnerable populations and life stages and on communication of results. It is essential that these topics be considered at the beginning of every exposure assessment.

I have reviewed this document from the point of view of regional risk assessments, of which I am often asked to provide an opinion or review. Many times these are currently conducted with methods and exposure factors from the 1990s. I have framed my review by assessing if this document would aid those risk assessors in improving their exposure assessments, particularly among vulnerable populations. In too many of the communities that I work in, the public does not feel that the exposure assessments reflect them and therefore do not accept the results and continue to live in fear of exposure and mistrust. The final version of this document should improve exposure assessments and communication in those communities that are most impacted by environmental contamination but often feel marginalized.

It is very important that this document replace the 1992 version. Anything important from the 1992 document that is still relevant should be included in this new updated document. This is particularly important if the vision is to make this a living document online that will updated more regularly and be reflected in ExpoBox (https://www.epa.gov/expobox).

It would be important to emphasize throughout that often the most uncertain part of a risk assessment is the exposure assessment. Thus, as new information becomes available that may reduce the uncertainty associated with the exposure assessment the risk assessment should be updated.

It is also important to highlight throughout that exposure assessment should be an iterative process. After a decision has been reached and risk mitigation efforts have been put in place, it is important to redo the exposure assessment to evaluate if exposures have in fact been reduced.

While occupational exposure assessment is not the focus of this project, it can be a very important component of aggregate exposures and should at least be mentioned where

appropriate so that exposure assessors may be reminded to consider occupational exposures in addition to community or residential exposures as necessary. While this document need not go through occupational exposure assessment techniques, it would be helpful to provide links or references of some of the many useful sources, such as the AIHA Book A Strategy for Assessing and Managing Occupational Exposures (Jahn et al., 2015).

The document provides an overview of many important topics in exposure assessment and then provides hyperlinks and references to documents for more details. I am concerned and curious how these will be updated and maintained. Already many of the links appear outdated and not functional. There should be a repository of the documents referenced available. Perhaps the EPA HERO (Health Environmental Research Online) can be used to facilitate this? (https://hero.epa.gov/hero/)

It is not always clear who the intended audience is. Is the document solely for regulatory decisions by EPA and other agencies, or is it intended to aid researchers that assess exposures as well?

In summary, I believe that these updated "Guidelines" take us one huge leap forward in the applied field of exposure assessment and will greatly improve regional risk assessments.

Nicole Cardello Deziel, Ph.D., MHS

This document represents a major advancement over the prior 1992 Exposure Assessment guidelines. The field of exposure science has moved toward more comprehensive and quantitative techniques for estimating exposure, which can substantially improve the risk assessment process, providing better understanding of exposure-disease relationships and better protection of public health. This document appropriately captures many of the advancements over the past two decades. It also incorporates important new topics, such as environmental justice and exposure assessment for vulnerable subgroups.

Overall, the document is well-organized, scientifically sound, appropriately referenced, comprehensive, and clearly written. It is a useful guide to practitioners of exposure science. For the most part, the document strikes an appropriate balance of describing overarching concepts and steps and providing references and resources for more specific, detailed guidance. Some exceptions regarding inconsistent level of detail are noted in my responses to specific charge questions. In terms of the scope, there is a missed opportunity to not incorporate or provide resources for some of the critical advances of the past decade to generate high-quality estimates of exposure, which include but are not limited to: statistical modeling (such as for exposures to mixtures), geographic information systems, sensors technology, the exposome paradigm, computational exposure science (including work being led at the EPA). In addition, the document could provide enhanced utility with a few more examples or illustrations (specific suggestions noted in responses to charge questions).

Penelope A. Fenner-Crisp, Ph.D., DABT

Intended audience: In the pre-meeting conference call, EPA said that the audience was primarily the exposure assessors, internal and external, who are preparing exposure assessments for use by EPA.

1992 Guidelines: "The Guidelines for Exposure Assessment (hereafter "Guidelines") are intended for risk assessors in EPA, and those exposure and risk assessment consultants, contractors, or other persons who perform work under Agency contract or sponsorship. In addition, publication of these Guidelines makes information on the principles, concepts, and methods used by the Agency available to all interested members of the public."

But, there also are additional audiences, as noted a decade ago when EPA began updating the 1992 guidelines. This presents a challenge to the authors who must identify and create the right balance in presentation: not too much, but not too little, information.

At the 2006 SAB consultation, which Dr. Parkin chaired, EPA stated that the user community consisted of EPA risk assessors in the Programs and Regions, EPA risk managers, and others, such as contractors and partners (e.g., other governmental organizations), the regulated community, and advocacy groups.

The Preface of the current draft document says the audience is "… exposure and risk assessors in the Agency and consultants, contractors or others who perform this type of work under Agency contract or sponsorship, as well as academic, industrial and others who perform this type of work in accordance with EPA policies and procedures. Risk managers/decision makers in the Agency also might benefit from this document because it describes approaches, defines terminology and summarizes methods exposure and risk assessors use."

So the intended audience has been expanded to include "outsiders" who perform exposure assessments using EPA approaches. And, maybe Agency risk managers. But no longer the "interested public?"

I would submit that Agency risk managers shouldn't be in the "might benefit" category, but should be in the "must read" category. They have an obligation to be familiar with the policies and practices that the staff/contractors who are preparing assessments are using, so that they (the managers/decision-makers) can reach sound, informed decisions. In fact, I would argue that all members of a team engaged in problem formulation, scoping and planning have an obligation to be reasonably familiar with the policies and practices of all of the technical disciplines involved (the exposure assessors, the hazard assessors, the mitigation specialists, the economists, etc.).

The "interested public" will remain an audience, even if not acknowledged as such. I would add internal and external peer reviewers of exposure assessment-related products to the audience. When someone is reading/reviewing a specific exposure assessment, s/he wants, and needs, to know "What were they (EPA) thinking? Is this assessment consistent with the principles articulated in the Guidelines? And, further, is this assessment consistent with the Program/Region-specific guidance that is applicable to the specific case study?"

So, in summary, there are several audiences for these Guidelines: 1) EPA exposure assessors; 2) Contractors performing exposure assessments for EPA, 3) Other outside parties performing assessments based upon EPA procedures, 4) Outside parties whose work is funded by EPA or others that may, or is likely, to be used by the Agency in its risk assessment/risk management process, 5) Other EPA technical experts, 6) Agency risk managers/decision-makers, 7) The "interested public, " particularly affected communities and regulated industries. This audience is heterogeneous and it is a challenge to find the right balance in presentation. But that's what internal and external review and public comment are for—to get feedback from each of these sectors. And, hopefully, that feedback will include comments on whether or not the draft Guidelines are enlightening and transparent. In finalizing these Guidelines, the Agency should ask itself "Are we issuing Guidelines that provide enough information for everyone?"

The draft document, as written, reflects feedback from internal (to EPA) peer reviewers, OMB Office of Information and Regulatory Affairs (OIRA) and other federal agencies. External peer review feedback is being sought from our Panel. Other external parties have submitted public comments to the docket. Hopefully, all of these sources will provide the Agency with valuable insights about whether or not the right balance has been achieved for all of the relevant audiences.

Christopher W. Greene, M.S.

My overall impression of this document is that it is a good source from which to apprise oneself of the current "state of the science" of exposure assessment. Its greatest strength is in the way it provides information from a large number of source documents in a single report.

Throughout my review, I asked myself whether the main focus of this document was on providing new information, or synthesizing/summarizing existing information from other sources. The document seems to rely heavily on citations of other sources, as evidenced by the long reference list. I see why this is necessary to keep the document to a manageable size. But in my view, this document needs more concrete examples to illustrate the concepts being discussed. Examples (either hypothetical or cited from actual exposure assessments) would do a lot to add value to this set of guidelines, and make them more than a summary of (and link to) the vast body of documents on the topic from EPA and other sources.

Another issue I had to resolve while reading this document was that of the intended audience. I expected this document to be aimed at the exposure and risk assessment community at large. In many places throughout the text, there are statements that are clearly intended for EPA staff; this affects the overall tone of the document and may make non-EPA readers less likely to embrace it as a useful source of guidance (which it most definitely is).

There were a few exposure assessment topics that, in my view, should be added to this document, or expanded. The determination of relative source contribution factors is important in allocating exposures among multiple sources in order to ensure that aggregate exposure does not exceed health benchmarks. This concept (or an alternative, if one exists) should be added to the document. See EPA (2000), Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health, EPA-822-B-00-004. The role of multiple exposure durations, and

the potential effects of shorter-term exposure assessment on longer-term exposure assessment, are also an important topic that should be expanded. Occurrence and monitoring of chemicals in the environment is mentioned early in the document, but not fully developed in later chapters. I also found some issues with the discussion of working with Native American tribes. These and other issues that deserve attention are outlined in the responses to charge questions, and in the "Specific Observations" table.

Other reviewers suggested the addition of a bulleted list of key points in each chapter, and also the addition of a glossary. I agree on both counts.

Michael A. Jayjock, Ph.D., CIH

In general I found this document to be a remarkably detailed, coherent and accurate explanation of what has become the vast state of the science of exposure assessment. The scope is very ambitious while the comments and insights provided within it represent a notable amount of accumulated wisdom born of extensive experience. I was particularly struck by the clarity and profound truth and implications of a sentence appearing in the first paragraph of the guideline:

"Exposure science characterizes and predicts the intersection of an agent and receptor in both space and time" [emphasis added]

It is important from my perspective is that these guidelines represent a very rich source of reference information on the critical factors driving exposure related to adverse human health effects from chemical exposure.

As mentioned above, a document of this type provides essential information as a reference for those conducting exposure assessments. Thus, it does not contain any primary conclusions that I could find. Indeed, there is no section on conclusions within the document, only an Executive Summary which does a credible job of summarizing the document without offering conclusions.

I suggest that the specific principles be identified and provided in 1 or 2 sentence bullets. Details on some of these bullets are provided below.

I agree with Mr. Greene and others that the liberal use of examples throughout the document would be most helpful to the reader. I also agree with Dr. Parkin that a glossary of terms should be included. This could be done using an existing glossary or glossaries as a template. The Agency should go through the document chapter by chapter to determine which terms should be included and then deciding on the specific definitions as a group project.

The following impressions and specific comments are offered for consideration by the authors in the spirit of continuous improvement.

- Specific areas of omission or recommended enhanced explanations are addressed below in the specific charge questions (Section II) and in the specific observations (Section III).
- I went through the references and attempted to open hyperlinks of interest to myself as an exposure/risk assessor. Quite a few of the links were dead or non-functional in that I got either

an error message or was not specifically directed to the web site or reference of interest. A complete listing of the links I tested and found dead is provided below.

- I could not find any information for downloading EPA generated physical-chemical models (e.g. ,, I-SVOC) which I have found critically important as sub-models for estimating or predicting exposures in indoor microenvironments.

Rebecca T. Parkin, Ph.D., MPH

The stated purpose for the draft Guidelines, a substantial update of the 1992 Guidelines, is to serve as a human exposure assessment resource for exposure and risk assessors in the Agency and among its consultants and contractors. It describes principles and provides guidance and references. Other purposes indicated during the public meeting included raising awareness about exposure assessment issues and guiding readers toward more explicitly recognizing and considering the issues during exposure assessment processes.

Overall, the draft is clearly organized, well-written and will be useful for many people in the intended audience. Important terms and issues are sometimes discussed at levels appropriate to achieve the stated purposes. The utility of the document would be improved by adding 1) a Key Points section (with points linked to the document's purposes) at the end of each chapter and 2) a glossary before the excellent References section.

- The document is largely accurate, although some sections would benefit from additional information and updated hyperlinks.
- While much of the draft is clear, important terms and concepts merit clarification. Specific concerns and potential remedies are noted below. Clarification of the audience for the entire document would facilitate a more even discussion of topics across the chapters. Figures which conflict with the text or are not clear need to be reconsidered (see below).
- The implied steps and the recommendations and advice provided are sound. Some chapters would be improved with further details. Concepts such as uncertainty, variability and communication appear in most chapters, however, making it challenging for someone interested in any one of these components to synthesize all of the advice provided.

P. Barry Ryan, Ph.D.

In general, I found the document to be well written and an excellent compendium of ideas and methods outlined for work in exposure assessment. The title holds true- Guidelines for Human Exposure Assessment. The "level" is perhaps 10,000 feet with broad strokes overviews of the various subjects on a chapter-by-chapter basis, but with some detail relevant to scoping, design, and implementation of exposure-related field investigations. The level is close to that of a "first-level" textbook on the subject, and USEPA may consider publication of the Guidelines in such a form. This could be supplemented by questions and problems sets similar to what might be found in current environmental health texts. It should serve the community well. Others in the review process did not care for this somewhat pedantic approach, but I found it useful for both the novice and expert alike.

The Guidelines contain an extensive bibliography that, while not meant to be exhaustive, does provide the reader with an excellent background in the material. Particularly noteworthy is the referencing of USEPA-authored documents. This extensive list could have been viewed as too inward-looking if it were not supplemented by an equally extensive list of non-USEPA references. I think the balance is quite good, keeping in mind the regulatory need and direction of USEPA as a policy-making Agency. I have some specific suggestions for making the USEPA work more useful below.

One may question the high-level view of the Guidelines as being insufficient to aid the researchers in developing and implementing an exposure assessment. For example, there is insufficient detail to tell the novice how to design a study. But in my view, that is not the purpose of this document. I believe its purpose is to give the novice- and the expert alike- a basic understanding of what the role of exposure assessment is and what must be considered in designing and implementing an exposure assessment study. The extensive bibliography of both USEPA documents and peer-reviewed literature mentioned above is the next step in the design process. The Guidelines reference almost innumerable studies that the study designer can use to develop his or her work. The purpose is not to give guidance on designing an investigation. Such an undertaking is beyond the scope of any particular document as the parameters for an investigation are too varied. This document does give an understanding of that which is important in designing a study, but it is up to the researcher to design and implement their own investigation.

The overall-impression question asks specifically about the accuracy of information presented, clarity of presentation, and soundness of conclusions. I found no glaring errors in accuracy in the document. I have pointed out in specific comment places where I think modification for completeness and clarity might improve the presentation; however, on the whole, I believe the document is well written and well thought-out. Since the document is a Guideline, soundness of conclusions is not an especially important component. Nevertheless, when a conclusion is required I saw little in the way of conclusions that are not well borne out by references and to quality thinking on the subject.

Alan H. Stern, Dr.P.H., DABT

The document, overall, is clearly written and logically organized. My main criticism of the report is that it is unclear to me how it is intended to be used. EPA (in response to my question during the pre-meeting call) says that the target audience is EPA scientists who will be conducting exposure assessments and risk managers who will be evaluating those assessments in terms of application. However, the information as presented in the document, particularly in the more technically oriented sections, seems to me to be too general to serve as a detailed technical guide to the individual aspects and tasks of exposure assessments, and not concise enough to serve as an annotated compilation of resources available for exposure assessment. For example, Section 4.3.7 is a relatively short survey of methods to take socioeconomic data into account in an exposure assessment. The specific models addressed in this section and their application may not be familiar to more scientifically oriented exposure assessors. For them, the explanation of these models will be insufficient for determining which models to use, and certainly for providing technical guidance about how to work with these models. The section is, however,

much more detailed then needed to make the point that socioeconomic issues impact exposure and that there are models available to address such impacts. Similarly, Sections 6.2 and 8.3 discuss methods, including quantitative methods such as Monte Carlo analysis, for addressing uncertainty and variability. An exposure assessor who has not carried out such analyses previously will not be able to carry out even one-dimensional, much less, two-dimensional Monte Carlo analyses after having read this section. Given that, it seems to me that the appropriate level of such a presentation should be to provide a brief summary of what such analyses can accomplish and provide citations for technical references. The level of detail presented in the document, however, is much more detailed, but the intended use of that detail is unclear to me. Similar issues arise throughout the document. In summary, EPA attempts to be trying to split the difference between a technical manual and an annotated list of useful tools, but as such, it is not clear how an exposure assessor would use this document. Perhaps a risk manager would find this level of technical detailed useful in holding discussions with exposure scientists, but if that is the intent, it should be made clear.

The document does provide a good overview of the issues that an exposure assessor needs to be aware of. And none of this is meant to take away from the utility of having a comprehensive overview. However, several points of the document go significantly beyond the level of overview, and the danger here is that a little knowledge is a dangerous thing in the sense that it may lead a novice to think that she or he is, having read the document, in a position to use sophisticated and specialized tools.

In addition, there is a significant amount of repetition in the document. For example, probabilistic/Monte Carlo analysis is discussed several times in different chapters. The use of QA/QC samples, field blanks, trip blanks, lab blanks is also discussed at least twice.

Clifford P. Weisel, Ph.D.

The Guidelines for Human Exposure Assessment document provides a broad overview of approaches to conduct exposure assessment for EPA personnel and others looking to understand the U.S. EPA approach. The chapters are appropriate and follow a logical sequence. The information provided is at a very basic level that could be readily defended, with a strong emphasis on having proper quality assurance/quality control steps included in any assessment done. Many of the fundamental concepts are repeated in each chapter, such as statements on the need to do a stage process to assess what level of information is available and whether collecting additional information will improve the risk assessment ultimately derived from the exposure characterization. This can serve EPA analysts who may not review the entire document, but only those chapters relevant to a particular problem. The methodology and data presented are for approaches that have been extensively used and validated. While the need for taking this type of approach is understood and appropriate, including a chapter on more recent developments for exposure assessment, such as using GPS tracking with cell phones, new sensor systems, consumer product modeling, etc., would be useful so EPA personnel would be aware of newer techniques as they become available for potential incorporation in their exposure assessment before the next version of the guidelines is developed.

The document provides the basic approaches that are to be taken for developing and implementing an exposure assessment for use in a risk assessment, along with identification of resources to find more information. This is a reasonable approach. However, the full target audience is not entirely clear. The level of detail across the chapters is uneven, so at times appears to be a primer to provide a basic understanding, while at other times a greater level of understanding is required. It is suggested that the guidelines strive to do the former to provide the basic knowledge needed to understand the field and approaches to do exposure assessment and guidance on where to locate the details necessary for any specific application. This can be accomplished by provide the basic approach illustrated with some examples. However, the examples are of uneven quality and not necessarily in sufficient detail to very useful. An alternate approach would be to have an appendix with several examples that cover multiple chapters for different media, contaminants and approaches (measurement, modeling) so that the user of the document could see how an exposure assessment is done from its concept to a full utilization in a risk assessment. Communicating the results to the variety of stakeholders in EPA and community groups is correctly highlighted, though more guidance and uniformity in how to do so should be provided. Understanding uncertainty and variability are highlighted as well in different chapters, however, the manner that they are interwoven in Chapter 8 could lead to confusion when uncertainty and variability of exposures are presented. Lastly, it is important to be consistent in how terms are defined and utilized through the guideline. The text should be reviewed to make sure that consistency exist and consideration be given to including a glossary that defines how they are used in the text.

IV. RESPONSE TO CHARGE QUESTIONS

Overview Comment

Question 1. Please comment on the overall utility of the draft Guidelines for Human Exposure Assessment to exposure assessors conducting traditional exposure assessments.

Paloma Beamer, Ph.D.

Compared to the previous version of "Guidelines" this document contains information on many topics not traditionally included by exposure assessors conducting "traditional exposure assessments." The document provides a good overview of these areas such as "probabilistic exposure modeling" and references the reader to the appropriate resources should they want to learn more. In general, in each chapter in the document touches on several considerations that the exposure assessor should consider and describes and justifies why they may want to. The document very clearly refers to other sections, but necessary topics are covered appropriately in multiple sections in case the exposure assessor only reads that one topic. The "Guidelines" are not a step-by-step guide, neither was the intention, but it is an excellent overview reference for the very broad topic of exposure assessment.

However, historically some affected communities have been marginalized during these "traditional exposure assessments" and there is still not enough emphasis on how to work with the community as a partner. This is essential for ensuring that the exposure assessment is representative of the affected community and will meet their needs. It is also not clear what the criteria or requirements are for determining which vulnerable population or lifestages should be included.

Many times communities are exposed to multiple chemicals simultaneously. For many of these chemicals there may not be much existing data or standardized methods to analyze samples. It would be very helpful if this "Guidance" documents could provide a brief overview of how to prioritize chemicals for assessment with references to obtain more detailed guidance. Similarly, it would be helpful to have an overview for how to develop an exposure assessment for chemicals with little to no data, analytical methods, or standardized protocols.

While this "Guidance" is not designed to advise the general public on how to conduct their own exposure assessments, key points for each chapter should be summarized so that a lay person could understand the purpose of each chapter. In the modern age, community members are often using online resources to analyze, understand, and critique how exposure and risk assessments have been conducted in their community. Making it so that the overall procedure is easier to understand should aid in building trust and transparency, while improving scientific literacy.

Although, there could be greater emphasis on the community for which the exposure assessment attempts to aid, if these updated "Guidelines" are followed by exposure assessors there is a high probability that exposure and therefore risk assessments will be greatly improved and more accurate in their estimations.

Nicole Cardello Deziel, Ph.D., MHS

This document will be highly useful to exposure assessors. It is most useful as a presentation of overarching concepts, considerations, and steps with specific resources and references for more detailed information. Inclusion of a table describing the major differences between this document and the 1992 document would be helpful, such as an expansion of what was presented at the External Peer Review Meeting. In general, the utility of the document could be improved with additional examples of real-world example calculations or conceptual frameworks within the document. An annotated existing exposure assessment included as an Appendix is one suggestion to enhance the utility. The utility and clarity would be improved with the addition of a glossary.

Penelope A. Fenner-Crisp, Ph.D., DABT

As the authors of this document point out, these Guidelines currently are designed to present overarching principles and policy, and not specific DIY instructions for conducting an exposure assessment. That is clear. It would not be possible for an assessor to conduct an assessment solely with these draft Guidelines in hand. That being said, I would submit that this document cannot be characterized as "Guidelines." This document currently is an overview of the current philosophy, general policies and points of view the Agency holds on exposure assessment, with a smattering of guidance here and there. In deciding what purpose this document is to serve, I believe the Agency has three choices: 1) To expand the current draft document to include adequate and specific guidance in each of the areas covered in the current draft. Only in this option could the document be characterized as Guidelines; 2) To strip the snippets of guidance out of the current draft document and re-name it "General Principles of Human Exposure Assessment," and, then, draft a companion piece that does, in fact, provide guidance for each of the topics addressed in the General Principles document; or 3) To strip the snippets of guidance out of the current draft document and re-name it "General Principles of Human Exposure Assessment," and refer readers to the Programs and Regions for their material that provides specific guidance for assessors in their respective areas.

If either Option 1 or 2 is chosen, the end product(s) must provide a description of, and "pointers" to *all* the key, relevant, more detailed guidance that the Agency has developed for general and Program/Region-specific use. This is not a suggestion to describe each piece of guidance in the text, but to assure that, at least, each is cited somewhere in a table, appendix, reference section, etc. The Agency has written many guidance documents over the years, and having a single resource to help an assessor/reader find them is essential. This also would assure that the reader consults only those publications that reflect the current positions of the Agency on an issue, rather than getting misled by accessing and reading out-of-date material. For the same reason, I second the Agency's position that the update should supersede, rather than serve as a complement to, the 1992 guidelines. If there is material of current and continuing value in the 1992 guidelines, it should be extracted and integrated into the update. The 1992 Guidelines should be archived and acknowledged only as history. This is the practice with other Agency Guidelines. For instance, you don't hear anyone saying "Go look at the 1986 cancer guidelines to see what we have to say about Topic X. No, everything that is current is in the 2005 Guidelines and the Children's Supplementary guidance that followed shortly thereafter.

What was the decision logic to have these Guidelines focus only on exposure in the non-occupational environment? By doing this, the Guidelines exclude discussion of a significant portion of the human exposure assessment activities of several Agency programs (i.e., OCSPP: OPPT and OPP; OLEM: OSRTI and ORCR). There really is no convincing rationale for excluding occupational exposure assessment. The general principles apply to both spheres, so it would be consistent and relevant in all three options. In the cases of Options 1 or 2, it would mean expansion of any discussion that currently provides specific guidance to include that which is unique to work settings.

What measures have been taken to assure that the guidance presented in these Guidelines is consistent with Program/Region-specific guidance and *vice versa*? There should be a statement somewhere in the document as to whether or not this step was taken, and if so, whether or not, there was consistency. If conflict, what steps will be taken to assure compatibility?

Christopher W. Greene, M.S.

To address "utility," I approached this question from the perspective of the work my colleagues and I do in the field of exposure assessment in the public health sector.

We look at exposure when we develop human health-based guidance values for contaminants in drinking water. Many of the contaminants we look at are present in consumer products, pharmaceuticals, food, breast milk, and other sources encountered by a large segment of the population. Because of the vast number of chemicals of potential interest, we must prioritize the chemicals we review; screening-level exposure assessments are one way we do this. There is not much material in the Guidelines about this topic specifically, but some of the content is relevant. One of the challenges we face is how to fairly compare multiple chemicals with varying amounts of available data. It is important to compare chemicals without penalizing chemicals for not having enough data, or for having too much data. This would be a good topic for these guidelines. In our exposure screenings we look at data on fate and transport properties, release potential, and environmental occurrence. While some of these topics are discussed in the guidelines, the discussion does not focus on the process of chemical prioritization.

When high-priority chemicals are reviewed for the purpose of developing drinking water guidance, the exposure assessment is expanded to include a relative source contribution (RSC) factor to account for exposures that are not related to drinking water, ensuring that an individual's total exposure from all sources does not exceed the threshold of concern. In addition to estimating exposures, this process requires some judgment when deciding how to manage exposures that are not common, but are much higher than the general population exposure—for example, exposures that are linked to behavior. To address these exposures, we sometimes consider the affected individuals to be outside the "general population" and decide to manage the exposures through messaging rather than incorporate them into the RSC value. (For example, we have taken this approach for certain algal toxins for which non-drinking water exposures from recreation or dietary supplements can best be mitigated by encouraging people to avoid certain behaviors.)

When our guidance development process is complete, we communicate the results to the public. We place a strong emphasis on the use of plain language and making documents accessible to individuals who have screen readers; the Guidelines offer some advice on plain language but do not say anything about accessibility. (This is discussed further below in the appropriate chapter's comments.) We also often struggle with how to communicate low confidence without sounding evasive; the public want us to say "your water is safe if the concentration is below X," and our messages often have to be more nuanced than that. The Guidelines provide some helpful information on communicating uncertainty that may be applicable in this area.

We also encounter exposure decisions where we need to communicate both risks and benefits—for example, a chemical may be present in breast milk, but the potential risks are very low compared to the numerous benefits of breastfeeding; exposure to DEET from insect repellent carries a risk, but also protects people from vectorborne illnesses. I would like to see this addressed in the communication section in the Guidelines.

Outside the realm of water guidance, at my agency, we also deal with cases involving pesticide misuse, which may involve spills, incorrect application rates, or most commonly, contamination of homes with pesticides that are not intended for indoor use. For such cases, the Guidelines provided a lot of good information on identifying the population of interest and potential exposure pathways. There was also some information on sampling, but one challenge that we often face with home cleanups is the great expense of laboratory analysis. This often requires us to divide the overall sampling plan into stages, where many samples may be collected but only a few are analyzed. Once the initial results come in, the various stakeholders discuss whether to continue sampling or to conduct additional cleanup and resampling. This avoids unnecessary lab work and its attendant cost. I did not see any discussion of this sort of iterative process in the Guidelines.

Michael A. Jayjock, Ph.D., CIH

As mentioned above, I find these guidelines to be a very rich source of information on the critical factors driving exposure related to adverse human health effects from chemical exposure. This represents an important resource to anyone doing exposure assessments. My sense is that the guidelines could have even more utility if more complete discussions are rendered on topics outlined below in review comments on the various chapters.

I agree with Mr. Greene that there should be some discussion about using exposure assessment to prioritize the risk from exposure to multiple chemicals.

I also agree with Dr. Parkin that there should be succinctly worded bullet points at the end of each chapter emphasizing the principles or principle guidance point made in the chapter.

Also, the document would be more useful if all of the links were tested (with date of testing before document is issued as final), and those that were dead were either eliminated or marked as to their status.

Some further specific comments on the above bullets are presented below under comments for specific chapters.

Rebecca T. Parkin, Ph.D., MPH

The draft meets the purpose stated in the Executive Summary (p. xiii, para. 2). The *Guidelines* generally provide a well-structured introduction to human exposure assessment, including discussion of key terms, concepts and issues. Bulleted sections presented at the end of each chapter introduction is a valuable orienting tool for readers.

A similar device, such as Key Points, would be a helpful tool at the end of each chapter. This final section would aid the reader in capturing the major points the authors want the readers to retain as they read on and as they practice exposure assessment. The current excessive use of "urgency" terms (such as need, critical, important, key, necessary - among others) throughout the draft makes it difficult to determine whether all of the items presented with these terms are of equal importance in the exposure assessment process. Editing out some of these terms may provide the reader with more nuanced guidance. In each chapter, identifying and highlighting the top few "musts" in a final Key Points section would make this document more useful to the reader.

Furthermore, some terms (e.g., stakeholder, community, variability and communication) are not consistently defined; others terms (e.g., community involvement, peer review and decision uncertainty) were found with varying descriptions in different parts of the draft. For some terms (such as sensitivity analysis) linked documents either did not include the quote or could not be retrieved using the links provided. A glossary of important terms could be inserted between Chapter 9 and References to foster congruent usage among authors, to ensure appropriate citations and to improve the reader's comprehension.

While Chapter 4 offers many helpful recommendations, such advice is less rapidly identified in several other chapters. Determining whether specific recommendations are or are not desirable in this manual would provide a basis for more comparable depth throughout the document and would keep readers' expectations at the same level across the chapters.

P. Barry Ryan, Ph.D.

As pointed out in my General Comments, I believe this document will be of great utility to the entire Exposure Assessment community. It offers a substantial compendium of knowledge and thinking in the science and will serve as an educational tool to the novice and a useful resource for the expert. Each of the Chapters details current thinking on the concepts of the science and can be used to hone the design and implementation for many different types of field investigations and modeling studies. In my opinion little is left out as all aspects of exposure science are covered ranging from the basic principles through communication of results. Again, it is not a roadmap for the design of any investigation, but rather a set of directions to guide the design, implementation, and analysis of such investigations.

Perhaps the most valuable aspect of this work in the fact that it is all in one place. The Guidelines compile data on all aspect of exposure science in one place affording easy reference and study. The document provides an excellent pedagogical text for a graduate course in exposure science including not only excellent discussion, but also an extensive bibliography needed for the novice to understand the principal concepts of the field. Further, it is somewhat encyclopedic and can be used as a reference document for the more experienced researcher.

The authors are to be commended for pulling together this diverse material and presenting it in a coherent fashion.

Alan H. Stern, Dr.P.H., DABT

As discussed in my comments under General Impressions, I do not think that, as currently structured, this document, particularly those sections that are more technically (rather than conceptually) oriented, would have direct utility to exposure assessors. Presumably, exposure assessors have that title because they have specific and detailed training in exposure science. Thus, they would be expected to have detailed knowledge and experience in those topics that would normally be part of a "traditional" exposure assessment. For them, these topics should not be new and the main benefit of having formal guidance on the various aspects of exposure assessment would be the standardization in approach, or the provision of minimal requirements for various types of exposure assessments. That is not, however, what the document provides. For less "traditional" aspects of exposure assessment with which the assessor may have little or no training, such as integration of socioeconomic data into the assessment, the text is not adequate to provide the necessary training to allow the assessor to confidently and competently apply those aspects. For novice exposure assessors or those in training, the text is, likewise, not adequate to provide more than an introductory survey of the necessary knowledge and skills. This guidance can be contrasted, for example, with the EPA's 2005 Guidelines for Carcinogen Risk Assessment. That document is largely geared to those who are familiar with technical aspects of risk assessment. It clearly points out critical decision points and provides specific guidance for those decisions. It also clearly lays out the EPA's policy and the conditions for diverging from the defaults. It can be argued that the Carcinogen Risk Assessment guidelines deal with a more circumscribed topic than the Exposure Assessment guidelines, and can therefore be more prescriptive. The difference between the focus of these two guidance documents, nonetheless, points out the problems with the intended utility of the current guidelines

Clifford P. Weisel, Ph.D.

The document is generally appropriate for EPA and scientists who are familiar with the broad with environmental science and risk assessment but not necessarily exposure science and assessment. However, who the actual target audience is, is not completely clear. The document strives to provide the very basics for planning/ designing, obtaining the data needed and conducting an exposure assessment either through modeling or measurement. Some examples of doing so are also given. However, I found the examples used of uneven quality with some being tangential to what was being discussed. Since the breadth of field precludes giving a prescribed approach that can fit all situations, it is important that the examples be more illustrative of

successful exposure assessment and of projects that were not successful. The approaches given are valid and the references to models, data and sampling needs provide exposure assessors with valid tools for conducting exposure assessments. That said, because of rapid changes in the field and new data and models becoming available rapidly, the document should be made more of a living document and a chapter highlighting new approaches and data should be included. The utility of the document could be improved by being consistent in the level of detail provided across chapters and making sure that terms used throughout were harmonized. The figures throughout the document should be reviewed for clarity and to determine if they are self-explanatory and consistent with the text.

Chapter 2. Principles of Exposure Science/Exposure Assessment - provides a review of exposure science concepts and principles, including approaches and tools, that can be considered when planning and conducting exposure assessments.

Question 2. Please comment on the completeness of the discussion of exposure science and its application to exposure assessment.

Paloma Beamer, Ph.D.

Chapter 2 provides a very complete discussion on the field of exposure science and its application to exposure assessment. Since 1992 this field has evolved very rapidly and the "Guidelines" will be a great resource for exposure assessors to understand the current state-of-art perspectives of exposure scientists.

This Chapter really highlights how and why "exposure science" has become its own discipline. For example, Figure 2-4 really highlights the new technologies that have been developed and demonstrates the multi-faceted and dynamic nature of exposure science. This Chapter also clearly lays out that the focus should be on the receptor rather than the sources of the stressor, which will challenge the paradigm of many "traditional" exposure assessments. However, this is essential because of the importance of human behavior and characteristics on exposure.

Additional topics that have been added to this draft that really ensure the completeness of the Chapter is the discussion on direct and indirect approaches and how observational studies and models go hand-in-hand, underscoring why it is important to consider both in your exposure assessment.

A very comprehensive and complete list of definitions is provided and nothing appears to be missing from this Chapter. If a traditional exposure assessor reads this chapter it will make them realize that there are many new updates to the field that they should be considering and why they should consider them. Essentially, this Chapter is so well written and organized, and the updates are well justified, that it is likely that exposure assessors will then go on to read the other chapters as appropriate.

Although the Chapter provides many updates on exposure assessment, the section on calculating exposure estimates is a bit too simplistic. This is particularly true for dermal exposure. While many of the exposure equations used by experts in the field may be more advanced by what is warranted for this chapter, references to those documents and updated definitions should be provided (Zartarian et al., 1997).

Even though dermal exposure has long been known to be underestimated (Zartarian & Leckie, 1998), assessors continue to underestimate this route of exposure. It would be important for the updated "Guidance" to discuss some of the more updated perspectives on dermal exposure and uptake (Zartarian et al., 2000), many of which are not even that recent. More detailed perspectives are provided in the comments section.

Zartarian V, Ott WR, Duan N. A quantitative definition of exposure and related concepts. J Expo Anal Environ Epidemiol 1997;7(4):411-437.

Zartarian V, Leckie JO. Dermal exposure: the missing link. Environ Sci Technol 1998;32(5):134A-137A.

Zartarian V, Ozkaynak H, Burke JM, Zufall MJ, Rigas ML, Furtaw EJ. A modeling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and nondietary ingestion. Environ Health Persp 2000;108(6):505-514.

Nicole Cardello Deziel, Ph.D., MHS

Exposure science is a field still struggling to define its nomenclature and its role both as an independent discipline and a component of other disciplines: risk assessment, epidemiology, toxicology, occupational medicine. As such, the current EPA document could be strengthened with a glossary. Some terms, such as "internal dose" or "dose" are defined slightly differently depending on one's field of expertise, so clarity about how EPA is defining terms would be useful. In addition, the document itself is inconsistent in certain use of terms, such as stressor vs. agent.

The concept of "mixtures" is indirectly mentioned on page 16. Can this be made more explicit and any further guidance or resources provided?

For example: http://www.niehs.nih.gov/about/events/pastmtg/2015/statistical/
http://www.atsdr.cdc.gov/mixtures/

This chapter provides the most simplistic equations. I recommend including the most complex equations and pointing out that terms could be dropped or assumptions could be made if data not available. For example, all equations could include a time component, and the dermal equation could include the dermal permeability coefficient with some discussion about resources for obtaining such values.

Page 23: The chapter's concluding paragraph is important, and it seems to be a missed opportunity to not expand or specify or provide links to some of the recent and emerging efforts to greatly advance exposure science.

Penelope A. Fenner-Crisp, Ph.D., DABT

This chapter covers the concepts and principles of exposure science from a high altitude view. Whether or not it's too high should become evident as one moves deeper into the document.

There are topics that I would like to see addressed that currently are not. The document states in the Preface that there will be no discussion of "…emerging topics such as high-throughput exposure assessment, the implications of *in vitro* based risk assessments on the field of exposure assessment, or the ongoing ExpoCast program…." Even though these tools are in the early stages of development and incorporation into the assessment process, with no standardized

approaches yet agreed upon. I believe there should be some discussion of their current scope, early applications and what EPA believes to be the promise they hold for the future. It would be a good test of EPA's prognostication abilities and a challenge to its ability to engage in forethought.

Secondly, other emerging topics not mentioned at all are the exposome and the Human Exposome Project or the relationships between exposure and microbiome(s) and the Human Microbiome Project.

Thirdly, these guidelines, by implication, appear to embrace the NRC interpretation of exposure science as extending "beyond the exposure event itself (i.e., the point of contact) to study and describe the processes that affect the transport and transformation of agents from their source to a dose at a target internal organ, tissue or toxicity pathway associated with a disease process" (NRC 2012). Given this scope, this places ADME within the realm of exposure rather than hazard/toxicity. However, there is virtually no useful discussion of ADME in the guidelines-just a brief mention here and there. If the Agency is, in fact, redefining exposure in concert with the NRC interpretation, then discussion of how ADME is taken into account in equations and models, availability of data and databases, etc. should be included, as appropriate, and relevant to each of the chapters.

Fourthly, there is no mention of the increasingly popular and implemented concept of adverse outcome pathways (AOPs) or the related analysis of mode of action (MOA). Exposure plays a significant role in the characterization of both AOPs and MOAs. Sufficient experience now has accrued with these two concepts that a discussion of the contributions exposure assessment makes to them is warranted here.

Fifthly, I agree with the other reviewers and commenters who argue that there should be discussion of consumer product exposures.

Lastly, how consistent are the descriptions, principles, approaches, etc. in these Guidelines with the efforts and outputs of the OECD Task Force on Exposure Assessment? Have the authors of the draft Guidelines examined the Task Force's reports and drawn upon them? EPA has had a significant role in the Task Force since its inception, in fact, even before that. OECD's 2013 publication *Guidance Document for Exposure Assessment Based on Environmental Monitoring Series on Testing and Assessment No. 185. JT03338684* covers much of the same territory as the draft Guidelines. It is available at:
http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2013)7&doclanguage=en.
OECD Activities on Exposure Assessment can be found at:
http://www.oecd.org/chemicalsafety/risk-assessment/oecdactivitiesonexposureassessment.htm

Furthermore, I agree with the other reviewers and commenters who argue that related activities going on around the world (Canada, EU, OECD, WHO, etc.) deserve coverage, and, perhaps, in some cases, adoption.

Christopher W. Greene, M.S.

The chapter provides a good overview of the major issues and concepts relating to exposure assessment. However, some important topics that are briefly mentioned in this chapter could be developed further, either in this chapter or in subsequent chapters. Section 2.3.3 includes a brief discussion of aggregate exposure. In practice, this is a complicated aspect of exposure assessment that often involves judgment on the part of the assessor and/or application of policy to allocate a tolerable exposure level among multiple sources. EPA has provided guidance on this in the form of a decision tree used for developing a Relative Source Contribution (RSC) factor.

The use of existing monitoring data is common when resource limitations preclude the generation of new data to answer a public health concern about exposure to chemicals in the environment. The chapter includes some reference to biomonitoring, but there is not much there on the importance of environmental monitoring in assessing potential exposure and prioritizing chemicals for further study.

The focus of the chapter is (rightly, I believe) chemical stressors, denoted as "agents." Although Table 2-1 allows that an agent may be biological or physical in addition to chemical, the chemical aspect gets the bulk of the discussion in the chapter. Although these non-chemical stressors are mentioned in Chapter 1 and mostly excluded from the discussion, it may be useful to acknowledge them in this chapter and discuss how they fit (or don't fit) into the paradigm of this document. Alternatively, the writers could restrict the definition of "agent" within this chapter to include only chemical agents.

I thought that the last sentence of the first paragraph of Section 2.3.3 was a good synopsis of the applications of exposure assessment, and could be developed further into its own section or even its own chapter, discussing what aspects or tiers of the exposure assessment process are likely to be useful for each application.

I also have several comments on definitions of terms, description of units of measure for some exposure-related terms, and provision of examples that would help to clarify some of the concepts. These are listed in the "Specific Observations" table at the end of this document.

Michael A. Jayjock, Ph.D., CIH

I believe that this chapter does a credible job of presenting the general concepts and principles of Exposure Assessment Science. I believe that Figure 2-1 does an excellent job of presenting the big picture of the source-to-health effects continuum. The chapter also seems to hit upon most of the salient topics under the topic of Principles of Exposure Assessment.

On page 18 the first equation for inhalation exposure is not complete. It calculates mass per unit time as the measure of exposure; however, this mass needs to be put into the context of the time period or duration of exposure over which it occurred. Without specifying duration, the exposure cannot be compared to a toxicological benchmark with the same dose metric (mass/time) and same or similar period of exposure. The same comment applies to the first

equation on page 19; specifically, there needs to be a time period of exposure for comparison with toxicological benchmarks.

From my perspective as someone who has conducted, written and taught about exposure/risk assessments outside of the specific realm of the EPA, I would have preferred to have seen more explicit and plain discourse on the some of the universal principle/issues that I perceive are extant and very important within the science; *viz.*,

- The need to appropriately trade conservatism for a lack of data or specific knowledge. This is the precautionary approach which is, or should be, universally applied when doing exposure/risk assessments. Note: this principle is hinted at and tangentially covered at within various places within the guidelines but, from my perspective, it is not explicitly stated or explained but should be.
- The critical need for exposure modeling in situations
    - You want to monitor exposures, but there is NO method available
    - You cannot measure exposures "right now" when they are occurring
    - You cannot measure exposures because you cannot be present, such as when they happen at another location, they happened previously (retrospective), or they have not happened yet (prospective)
    - A small sample size of exposure monitoring events leads to a heavy bias toward concluding unacceptable exposures are acceptable
    - The financial burden associated with collecting sample and analytical fees are real-world challenges that restrict monitoring efforts
- The vital distinction between sources originating within the near-field (residence or arm's-length during activities) versus traditional far-field sources (*e.g.*, cars or emission stakes). In this regard, I believe that the guideline should highlight the significance of Lance Wallace's TEAM project work on the relative dominance of near-field sources relative to human exposure to chemicals.
- The almost inextricable meshing of variability and uncertainty within any uncertainty analysis. Again this topic has some voice within the document but, I believe, should be further developed and explained as an educational or guidance piece for exposure assessors. See my review comments on chapter 8.
- As another aspect of the precautionary approach, one can tolerate much more uncertainty in an exposure assessment when the toxicological benchmark(s) indicates a relatively low level of potency vis-à-vis the anticipated worst case range of exposures.
- The need to match both the exposure or dose metric and the time period of exposure with the dose metric and time period of toxicological benchmarks. BTW: Neither dose metric nor exposure metric is defined within the guidelines and should be.

Rebecca T. Parkin, Ph.D., MPH

The discussion of exposure science and its application to exposure assessment seems to be complete for meeting the *Guidelines*' intended purpose. Definitions of exposure and dose are introduced, and important concepts related to exposure assessment and risk assessment are discussed. Exposure assessment methods and techniques are noted. Sections 2.3.3 and 2.4 are particularly helpful in orienting the reader.

Some clarifications would improve this chapter; to begin with, there are discrepancies in several terms. For example, the definition of "exposure science" on p. 4 does not mention prediction, as is included elsewhere (pp. 1, 8 and 9). Given the footnote on p. 2, the omission of "stressor" in Table 2-1 is puzzling. The mention of "toxicity test" on p. 12 is new to the reader; this term should be defined or footnoted for readers who do not know what such a test involves or does.

Figure 2-3 is a valuable complement to the text. If the last sentence in 2.3.3 (p. 16) is an overarching statement and not applicable to cumulative exposure assessment alone, then it may be better placed at the end of the second paragraph of 2.3.3 (p. 13). If this sentence applies exclusively to cumulative exposure assessment, then it should be revised to reflect that limitation.

In Section 2.4.1 (e.g., first equation of page 18), the omission of exposure duration is a regrettable oversight. This concern needs to be addressed here and elsewhere before the guidelines are finalized.

The last paragraph of this chapter is not helpful to the intended reader. A summary of key points would be more useful than looking toward the future. Forthcoming data, measurement techniques, models, etc. would be better placed in an appendix to this document. This new section would provide a means for readers to increase their awareness of these potential issues without making the document itself more difficult to understand.

P. Barry Ryan, Ph.D.

Chapter 2 Principles of Exposure Science/Exposure Assessment presents a solid and complete introduction to exposure science in concise form. It is densely packed, but still quite readable. I think this Chapter may be the most important in the document as it sets the stage for the rest. Hence, it should be made as hard-hitting as possible. It has succeeded quite well in this regard, but there is always room for improvement.

Definitions have been a problem in exposure assessment since it first began to be recognized as a separate science. However, consensus has now been reached and definitions recognized be all. The Chapter presents them in a clear and concise fashion, referencing many relevant documents and manuscripts to support the terms. Even among the review panel, there were concerns about the definitions used- in particular, delivered dose and effective dose were of concern. However, the references to Zartarian's work on exposure definitions has become the watchword in the field of exposure science. I think the document holds well to these definitions.

I express a small amount of concern regarding attempts to expand or contract definitions of "agents" and "stressors." I believe a scientists we must harmonize these definitions and work towards a basic statement on what should be considered part of the "exposure assessment paradigm" as a component of the risk assessment paradigm, especially within the internal confines of this work. I believe that the "stressors" definition may be more closely aligned with the general concept of exposure assessment, namely "agents" that lie somewhere along the line of health outcomes in terms of either a direct effect, a modifier of effect, or a confounder of

effect. All should be in the purview of the exposure scientist as all of these considerations are of interest in the design and implementation of field investigations of exposure.

The definitions are followed by the overall concepts of exposure assessment and, in particular, where it fits in with the full Risk Assessment paradigm. Perhaps key to this segment of the Chapter is the discussion of variability and uncertainty in general and how it applies to exposure assessment. The differences between population variability and uncertainty is laid out quite clearly and includes approaches for addressing the uncertainty associated with lack of knowledge of the components of computational exposure analysis. This section is very brief, but is the first I have really seen that attempts to address these issues. I think the document would be served well by expansion, but later sections address some of the computational issues.

I particularly liked the figures and diagrams presented in this chapter and would encourage their use in pedagogical applications of the chapter content. The conceptual models developed afford an organization of the thinking associated with the exposure analysis paradigm.

I was disappointed by the last paragraph in the presentation regarding "looking forward." The content is completely speculative and has little support via references and documentation. It is quite short and limited in scope. The authors may wish to expand this substantially, or leave it out altogether. I believe others expressed similar sentiments regarding this section of the chapter and suggested further amplification.

Alan H. Stern, Dr.P.H., DABT

This chapter is clearly written and provides a useful introduction to exposure science in general. It is complete in terms of introducing the major concepts in exposure science. This would be an excellent stand-alone section.

Clifford P. Weisel, Ph.D.

The chapter on principles of exposure science/assessment provides a basic background on the terminology used in the field and a rationale for conducting an exposure assessment. The chapter is based on the framework outline in the recent NAS Report on Exposure Science in the 21st Century. It follows the traditional definition of exposure, being the external contact and once something enters the body it becomes a dose. With the strong utilization of biomarkers for understanding exposure, the development of the exposome, and metabolomics as a tool in exposure science, our current state of exposure science lies along the continuum between exposure and health effects is less distinct (see Lioy and Weisel, Exposure Science: Basic Principles and Applications 2014). The chapter discusses the need to understand the various types of stressors that people are subjected to (e.g., non-chemical stressor) and that real world exposures are typically multi-contaminant, multi-media and multi-pathway. These considerations should be emphasized throughout the document and I suggest that a section entitled Multi-pollutant or Multi-media be included in most chapters. The importance of lifestages on exposure is introduced in this chapter and appropriately has a distinct chapter in the document.

The different routes of exposure are described and the need to understand the differences in uptake and effects by route is outlined. The role of direct and indirect approaches to characterize exposure is appropriate outlined, as are some of the caveats in understanding biomonitoring. The equations need to be reexamined as they are in the most simplistic form with a number of inherent assumptions that eliminated some terms which may not lead to a complete understanding. See equations in 1992 document as a starting point.

The use of a Tiered Assessment, starting with screening level analyses to more complex measurement and probabilistic modeling are outlined. Differences between aggregate and cumulative exposure and the need to characterize uncertainty and variability are discussed briefly. The need to understand the differences among the three exposure routes relative to duration/frequency is presented along with simple equations for the exposure estimation from each route.

The statement that inhalation exposure is assumed equal to dose for gases, aerosols and fine particle <2.5µm is not correct for all contaminants, as the lung barrier is not 100% permeable for all species and agents can deposit in different parts of the lung dependent upon their solubility in lung fluid, which alters the systemic dose. I suggest that this statement be revised to reflect the need to determine the permeability of the specific species being examined and where in the lung it deposit. For example highly soluble acid gases affect the upper respiratory region.
The statement that gases generally produce very low dermal exposures is not correct for the gas phase of some semi-volatile compounds (e.g., Weschler, C. J.; Nazaroff, W. W.SVOC exposure indoors: fresh look at dermal pathways Indoor Air 2012, 22 (5) 356– 377, DOI: 10.1111/j.1600-0668.2012.00772).

Chapter 3. Planning and Scoping and Problem Formulation - describes a process for planning, scoping and problem formulation for an exposure assessment. It emphasizes the importance of: establishing goals and objectives; building an interdisciplinary team; developing a conceptual model; identifying assessment options, available resources and data needs; producing an overall assessment plan; engaging and involving appropriate stakeholders; engaging and involving the community; establishing data quality objectives; and the importance of peer review.

Question 3. Please comment on the content, organization, and presentation of the planning and scoping and problem formulation chapter.

Paloma Beamer, Ph.D.

In general, this Chapter clearly articulates all of the important steps and topics that should be considered at the onset of an exposure assessment. However, exposure assessments are typically conducted because a "potentially" identified community has been identified. Exposure assessments are much more efficiently and effectively conducted when they meet the needs of the community. Yet, there is no discussion of conducting a needs assessment or understanding the community's risk perceptions as an essential part of the problem formulation. Minor edits throughout this Chapter could be used to change the tone from "something we are doing ***to*** communities" to "something we are doing ***with*** communities".

Although, Section 3.1 (Interactions with communities) does acknowledge the importance of informing the community and involving the community, more emphasis could be placed on consulting them from the beginning and involving them as a true research partner. It is important to know if the community has concerns that differ from the exposure assessors so that the results can be more effectively communicated back to them.

The community is also a key informant, as many times they may identify contaminant sources or exposure pathways that would not occur to an exposure assessor who is not from that community. It would be helpful to provide "Guidelines" on how to work with a community to obtain this information. For example, you could start with a conceptual model of exposure pathways and ask the community through meetings or focus groups if there are additional ones that should be considered. If the concerns of the community are not addressed or answered by the exposure assessment, then they may continue living with those concerns long after the exposure assessment has been completed.

This chapter would benefit from examples of a conceptual model (similar to the one in Chapter 5), and a clearly defined "exposure problem."

It should also be highlighted more in this Chapter the importance of considering multiple environmental media, mixtures of chemicals, and multiple exposure routes & pathways are the problem formulation stage.

It is important to highlight that this chapter is a vast improvement over how the process of problem formulation has been described in the past, and these comments could be addressed with some relatively minor changes.

Nicole Cardello Deziel, Ph.D., MHS

This is a very important and useful chapter with a lot of critical information. It provides many resources and questions for consideration without being overly prescriptive.

Presentation of a conceptual model in Section 3.2.2 would be helpful. The conceptual model presented later in Chapter 5 (Fig 5-1) could be included here as well (or an alternative conceptual model).

Section 3.4 Communication strategies: An example of strategies for engaging with the community or the types of questions to ask at this stage them would be helpful. As noted by Dr. Parkin and Dr. Beamer, perhaps a more cohesive presentation of the communication strategies should be included in the document.

I agree with Dr. Weisel's comment that this chapter should include some discussion about addressing exposures via multiple media, routes, and to multiple contaminants.

Penelope A. Fenner-Crisp, Ph.D., DABT

This chapter would be a good place to remind the reader that most of the decisions EPA makes are risk-based, not hazard-based. That places exposure assessment on the same plane as the hazard assessment. More than one NRC committee has noted that problem formulation must include an *early* (emphasis added) consideration of the relevant exposure scenarios/pathways along with potential options for managing or mitigating the exposures (NRC 1996, 2009). Actually, one could make the case that exposure assessment is first among equals, for, if the exposure scenarios and population parameters are not characterized properly prior to beginning a risk assessment, one can end up with a product that is not useful to the decision-maker. This has happened on more than one occasion in the past at the Agency, leading to significant criticism from both internal and external sources.

I'd question whether this chapter presents an overview of Planning and Scoping and Problem Formulation at an adequate level of detail for all of the topics covered here. I have special concerns on the topics of the Community Involvement, Conceptual Model and Communications Strategy.

With regard to Section 3.1.3. Public, Stakeholder and Community Involvement, the EPA references (EPA, 2003f, 2011i, and 2013) took me nowhere. The EPA 2003f link in the reference section did not work. The other two citations had no links. Only the EPA 2007b link worked.

This is such an important element and is an area where EPA has long and often been criticized. Two possible remedies: Add more text and create hyperlinks that work.

In Section 3.2.1 Individuals/Lifestages/Groups/Populations, the authors cite several publications on "Guidance specific to assess differential exposure due to occupation is available from several sources (Ignacio and Bullock 2006; Jayjock et al. 2000; Keil et al. 2009)." Both OPPT and OPP have guidance for occupational assessments, as I'm sure OLEM does as well. They should be cited here, even though OCSPP cites are noted later in the document.

Section 3.2.2 Conceptual Model would benefit from including a figure depicting an example of an actual EPA-developed Conceptual Model. It should be introduced in this section, rather than in Chapter 5. And, rather than the figure being of an ASTDR model, it should be one that EPA has developed.

Three good examples are Figure 1-2 Schematic of Human Exposure Pathways for NMP, found on page 27 of OPPT's 2015 TSCA Work Plan Chemical Risk Assessment. N-Methylpyrrolidone: Paint Stripper Use. Page 27. Available at: https://www.epa.gov/sites/production/files/2015-11/documents/nmp_ra_3_23_15_final.pdf

or

Figure 2-3. Example of a Generalized Conceptual Model with Examples of Possible Dimensions and Linkages in *Framework for Human Health Risk Assessment to Inform Decision Making* (EPA 2014b).

or

Figure 2 General Conceptual Model of the Potential Risks from Pathogens in Land-applied Biosolids in *Problem Formulation for Human Health Risk Assessments of Pathogens in Land-applied Biosolids* (EPA 2011, page 29). Available at: https://www.epa.gov/biosolids/problem-formulation-human-health-risk-assessments-pathogens-land-applied-biosolids and https://www.epa.gov/sites/production/files/2018-11/documents/problem-formulation-hh-risk-biosolids.pdf

I would take issue with the inference on page 35, paragraph 2, lines 1-2 that the hazard assessment should/would precede the exposure assessment. I think this runs counter to sentiments expressed in at least two NRC reports (NRC 1996 [Understanding Risk] and 2009 [Science and Decisions] and other authors (e.g., Pastoor et al 2014 [Pastoor TP, Bachman AN, Bell DR, Cohen SM, Dellarco M, Dewhurst IC, et al. 2014. A 21st century roadmap for human health risk assessment. Crit Rev Toxicol 44 (suppl 3):1–5]. I, too, would submit that a risk assessment should start with exposure rather than toxicity or, if the timeline and availability of resources demand it, conduct the exposure and hazard assessments in parallel with frequent cross-communication.

In discussing Planning and Scoping, it should be emphasized (over and over, if necessary) that this step for exposure assessment should not be carried out in isolation from what is being developed for hazard identification/dose response and other elements such as mitigation technology. Collaboration early and often is the key.

Section 3.3.1 Data Sources, Gaps, Limitations and Quality Objectives notes that "The analysis plan also specifies data quality objectives (DQOs) and quality assurance (QA) measures for all data used in an exposure assessment" and cites the *Guidance on Systematic Planning Using the Data Quality Objectives Process* (U.S. EPA 2006e). This guidance addresses some but not all of the issues and challenges related to data quality and usefulness.

In recent years, the National Academy of Sciences, in a series of reports, has advocated for the implementation of a systematic review process for all information that would/could be used in risk assessment (IOM, 2011 [Finding What Works in Health Care: Standards for Systematic Reviews]; NRC, 2011 [Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde]; NRC, 2014 [Review of EPA's Integrated Risk Information System (IRIS) Process]. NTP's Office of Health Assessment and Translation already has developed and implemented guidance on how to do this (NTP 2015. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration) and others have published on their approaches to systematic review (e.g., Woodruff TJ, Sutton P. 2014. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect 122:1007–1014 and EFSA (European Food Safety Authority) 2010. Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA J 8(6):1637, doi:10.2903/j.efsa.2010.1637). I am aware that there is activity underway in the Agency to develop systematic review principles, guidance and practices for use within certain programs and across the Agency. While this work is not complete at this time, it would perhaps be useful to introduce the topic in these Guidelines, offering some insight as to how systematic review might be applied to the selection and evaluation of exposure information.

Section 3.4 Communication Strategy is virtually useless as currently written. EPA's attempts to communicate its activities and actions have long been criticized as inadequate, too infrequent and not transparent. That being said, this section requires beefing up with greater detail on what will be shared, when and how. Or, if the authors believe that Chapter 9 covers this topic adequately, then they need to make reference to it here, along with some brief "talking points," so that the reader understands that this is not all the Guidelines have to say about Communication. Chapter 9 focusses mostly on how to communicate about the exposure (and risk) characterization, and not about their individual components. If the authors believe that the Agency would do and say something different about these early products of the exposure assessment and characterization, then here is the place to present that information.

Christopher W. Greene, M.S.

"The goals of the exposure assessment determine its scope." (p. 27) Well said, and that would make a good opening line for Section 3.1 or the whole chapter. Overall, this chapter is well organized and effective. Like the other chapters, it might benefit from some concrete examples of what the various elements, e.g., goals, questions, tiers, etc., look like in real life.

The Problem Formulation section (3.2) was well written and organized, but there is one key concept that seemed "buried" a paragraph on population groups. On the top of page 34, the text

mentions "establish[ing] a dialogue with toxicologists/health scientists." This is of key importance in identifying populations of concern and can have a major effect on the outcome of an assessment, or on the development of a standard or guidance value for water or air. I would recommend un-burying this and making it the basis of a separate paragraph in this section.

There are also some places in this document that suggest (without explicitly saying so) that this document is intended for EPA scientists conducting exposure assessments within some sort of regulatory framework. I don't believe that is the actual intent of the writers, but (for example) the document mentions regulatory requirements at the bottom of page 28, requirements which I assume apply to all EPA assessments, but might not be applicable to outsiders. Also, on page 32 the document lays out peer review requirements that appear to be EPA-focused, and the last sentence of the chapter advises readers to "consult with their programs." The document might benefit from some discussion early on about the intended audience. Does EPA expect/encourage non-EPA organizations and agencies to use this document? I know the answer to that question is affirmative, but the document does not always come across that way.

Under the heading of Overarching Considerations (Section 3.1.2), I would suggest including aggregate exposure, which can be addressed with an RSC factor with a reference to EPA's guidance on that subject.

Numerous minor comments are provided in the table at the end of this document.

Michael A. Jayjock, Ph.D., CIH

Planning and scoping and problem formulation are clearly critical elements for any exposure assessment done under of the auspices and regulatory context of the EPA. I have to admit to very little experience in this particular realm except in the limited sphere of relatively narrow assessments for clients. In my reading of this chapter and thinking about the issues covered, it appears to be complete from my perspective. I appreciate the organization, especially Figure 3-1 in aiding and educating the reader in viewing the specific elements of this process.

Indeed, this chapter highlights one of the areas where the experience and historical collective wisdom of the Agency is shining forth. I particularly appreciated the discussion on overarching considerations that include: aggregate exposure/RA, children's exposure/RA, cumulative exposure/RA, and exposure/RA for environmental justice. Sustainability is also mentioned as an overarching consideration; however, it only appears to be mentioned and applicable to the realm of tribal exposures. Perhaps this should be specifically mentioned or qualified in this context.

I agree with Dr. Stern that the primary question or questions to be addressed within the exposure/RA should be brought forth during this stage.

It is my habit as I read the document to make comments in the margins for areas in which I believe I have something to say relative to the text. I have very few comments in this chapter except for mostly editorial observations which I have entered below. I believe this reflects both my lack of experience in this area and the wealth and quality of the information presented.

Rebecca T. Parkin, Ph.D., MPH

The title of the chapter does not reflect that analysis planning and communication strategic development are also covered. A more inclusive title would be better.

Content: Overall this chapter provides a substantive orientation to and discussion of planning, scoping and problem formulation related to exposure assessment. Figure 3-2 is commendable for showing communication throughout the risk assessment process.

Clarifications and updating of information in this chapter, however, would improve specific sections. At the beginning of Section 3.1 (p. 26), clear definitions or descriptions of planning and scoping separately, as stated in the pre-meeting conference call, would strengthen the reader's understanding about the elements which distinguish these two phases. In 3.1.1, the mention of clearly stating the underlying question or hypothesis of interest, which is the basis for the goals and elements of the exposure assessment, cannot be under-emphasized. In fact, this issue should be included in the introduction of Section 3.1.

In the summary paragraph at the end of this section, "risk communication" is introduced for the first time; no new concept should be introduced in a summary. This concept is not used again until Chapter 9.

The four overarching themes noted at the beginning of Section 3.1.2 are not evenly treated throughout the document. While the first three are discussed in Chapters 2 and 4, sustainability is only briefly mentioned on pp. 6, 49 and 60. This theme deserves additional discussion if the Agency considers it overarching in exposure assessment; if not, say why not.

Section 3.1.3 provides information about involving communities and stakeholders in exposure assessment. It admirably points out that communications need to start early in the process and involve finding out how communities and stakeholders perceive fundamental concepts (e.g., risk, exposure, uncertainty), what they want to know and how they want to receive the results. But there are differences within this section and with other parts of the draft; particularly, "communication" sometimes seems to include "dialogue" and sometimes not. "Dialogue," one method of "communication," is used in Chapters 4 and 7, while "engaging" and "involving" persons are used in Chapters 3 and 7. None of these terms were found in Chapter 9. Additionally, "stakeholder" appears with a variety of definitions, sometimes including "community" and sometimes not. These definitional confusions occur in EPA documents as well. The authors of this document are advised to determine and state clearly which definitions of "community" and "stakeholder" they will use throughout all chapters. Further, the definitions in Box 3-1 cite one source (EPA 2011i) which is not currently available online and another source (EPA 2007b) which is linked to a general page without ready access to the definitions shown in the box.

The conceptual model shown in Chapter 5 (Figure 5-1) or a similar figure would be a valuable addition to Section 3.2.2.

Section 3.4 has little substance; it needs significant updating and expansion. The benefits of developing a communication strategy early in the assessment are considerable and merit more emphasis here. This section could be the "anchor" for all communication elements in this document, or Chapter 9 could be retooled as a comprehensive discussion of communication strategies and implementation throughout exposure assessment. EPA has more recent, sound advice; e.g., its January 2016 revision of the Superfund Community Involvement Handbook. Chapter 2 in this handbook has a good description and valuable information about developing communication strategies. (The more recent handbook link on August 7, 2016 was https://www.epa.gov/superfund/community-involvement-tools-and-resources. This should replace the EPA, 2005g citations and item in the Reference list.) A succinct and valuable Communication Strategies tool, with worksheets, was at https://semspub.epa.gov/work/HQ/174743.pdf on August 7, 2016. This resource is worthy of citation in this document.

Organization: The chapter is clearly, logically organized; readers will be able to follow the progression of thought with ease, although the last paragraph on p. 38 seems to be misplaced.

Presentation: While many issues are presented well, some need revisions. For example, Figure 3-1 does not entirely match the text or Figure 3-2. The text on p. 33 states that problem formulation builds on planning and scoping, but does not indicate that it feeds back to this earlier process as shown in Figure 3-1. Section 3.3 says that the analysis plan is part of problem formulation; it is not shown as such in Figure 3-1. Further, communication strategy is shown as part of the analysis plan, which is not entirely correct. Perhaps the figure is meant to show how the chapter is laid out but, in fact, it conflicts with the text and is not a useful aid for the reader. Are the key steps in a necessary sequence? This figure could be deleted. Figure 3-2 is more informative and accurate.

P. Barry Ryan, Ph.D.

Chapter 3. Planning and Scoping and Problem Formulation, as the name might suggest, offers a description of how one might go about designing an exposure assessment investigation. While much of the content might seem to be "common sense," as someone once said: common sense is not very common. The Chapter presents a compilation of a number of ideas and documents, processed through the collective experience of the senior scientists who are co-authors and thus offers, once again, the novice and the expert alike a pathway to study design. Many of us have learned such concepts through trial-and-error and this document bypasses some of the errors often made in study design. By following this framework on would be much more efficient in developing protocols for such an investigation, keeping in mind that the document does not purport to design studies, but rather give guidance on what proper considerations might be.

Figure 3.1 gives the essential content of the Chapter and the design phase of such an investigation. In particular, the bullet points under Key Steps are the design criteria in a nutshell and even senior investigators would benefit from adopting the step-by-step processes outlined. Such ensures covering all of the essentials without leaving anything out.

Probably the most important part of the Chapter is the emphasis on peer- and stakeholder-review in developing studies. Stakeholders have a "stake" in all studies as the results will likely influence how they live their lives from that time forward. Peer-review is more arms-length and thus is a more dispassionate look at the design and implementation strategy. Each has its place and should be considered. The Guidelines emphasize the need for evaluation by outside individuals as a necessary component of the design. The authors further emphasize the need for developing a conceptual model of an investigation. Again, this comes under the general rubric of clarifying and codifying what is to be done and why in an investigation- common sense perhaps, but something that is not always implemented.

At this point, I would recommend an expansion of these thoughts as a monograph or pamphlet of some kind, although reference to this document may suffice. A document of 20-30 pages issued separately may be of significant use to the community,

I believe the organization is adequate in this Chapter. The authors take us through a generalized overview and then on to specifics. They present sub-sections in the order they likely would appear in a study plan; these authors have developed many such plan in the past. I can offer no alternative that would do a better job.

Alan H. Stern, Dr.P.H., DABT

This chapter is reasonably comprehensive and reasonably organized. In Section 3.2.1, however, the concepts are not clear (e.g., scenario- based approaches, population-based approaches, individual risks) and require more specific definitions – perhaps some examples for each.

Since exposure assessments would rarely be generated as a stand-alone effort, but rather as part of an overall assessment of risk (or potential for risk), it is important to emphasize in this chapter that toxicologists/risk assessors should be brought into the exposure assessment process early in the scoping phase.

The key primary and key point in scoping, planning and problem formulation should be clearly defining the question that one needs to be answered – i.e., the first question should always be, "What is the question." This point needs to be emphasized in the document.

In Table 3-1, it is not clear why concurrent environmental sampling (e.g., stationary air sampling) is not included under 'Environmental Data'.

The application of the term, microenvironment, here is too limited in scope. This term has also been used to refer to the intersection of location and activity – e.g., the kitchen while cooking, personal air space while cleaning, running outdoors etc.

Clifford P. Weisel, Ph.D.

This chapter is organized in a reasonable fashion. It highlights the need to first define the problem and sequentially identify approaches to conduct the exposure assessment, including understanding the boundaries of the exposure to be evaluated and resources that might be

needed. It emphasizes following a tiered approach to first determine the scope of the problem by doing a screening analysis and to establish if a full exposure assessment is warranted. This is followed by adding more complexity as required to conduct a full exposure analysis, with the caveat that resource constraints be considered. Though understanding the strengths of each tier should be recognize, more complex tiers are not always better.

One suggestion is that the following questions also be included in the first paragraph of 3.1.1., which list a series of key questions to consider in the planning:
1) Should measurement, modeling or combination of both approaches be used?
2) What are the boundaries of the exposure?
3) What resources and tools are available?

The inclusion of Overarching Consideration can provide feedback on issues that EPA currently is focused on. While this has some merit, it is suggested that it be presented with a caveat that the issues that EPA should be address broadly can change with time. Thus, if this section is included it should be subject to review and revision on a regular basis (every 2-3 years) to reflect current concerns.

The section on Public, Stakeholders and Community involvement is an important component of the planning protocols. Make sure the text emphasizes the importance of involving the community and stakeholders as partners in the process and not dictate to the community.

This chapter does not explicitly discuss how to address multi-media, multi-route, multi-contaminant and non-chemical stressors, which were highlighted in the previous chapter as important considerations in a complete exposure assessment and part of the NRC recommendations. These need to be considered in the planning stages to adequately understand the full potential exposures and risk. For example, the risk assessment done for methyl tert butyl ether (MTBE) as an oxidative additive to gasoline did not adequately consider all exposure pathways and routes, which led to unwanted exposures through drinking water systems.

Chapter 4. Consideration of Lifestages, Vulnerable Groups and Populations of Concern in Exposure Assessments - discusses how lifestages, vulnerable groups and populations of concern could be at increased risk for adverse health effects from environmental contaminants due to disproportionate exposure or varied responses to exposure, or both. This chapter invokes existing Agency guidance, along with examples of case studies, to discuss where techniques and considerations associated with lifestages, vulnerable groups and populations of concern can be applied in exposure assessments.

Question 4. Please comment on the content, organization, and presentation of the information on lifestages and populations of concern.

Paloma Beamer, Ph.D.

The addition of this chapter to the document is very exciting and demonstrates how far the field has come. Furthermore, the addition is important because certain populations are not only more likely to be exposed to higher levels of contaminants, but they may be more vulnerable and susceptible to the health effects.

EPA is mandated by several Executive Orders to consider lifestages, vulnerable groups and populations of concern in exposure and risk assessments (Box 4-1). It is important to remind risk assessors of these legal mandates and requirements as part of this Chapter, and perhaps in some of the other Chapters as appropriate. It is not just important to consider these populations because of their vulnerability, but it is actually a legal requirement and this needs to be emphasized more clearly.

Section 4.1 should be retitled to make this clear. For example, "Presidential Executive Orders and Agency Policies Mandating Consideration of Lifestages, Vulnerable Groups, and Populations of Concern in Exposure Assessment." The purpose of this section should not be to provide a "history" but to document and remind exposure assessors of the legal mandates that require these populations be considered.

"Executive Order 12898 Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations" needs to be added to Box 4-1.

Although it is acknowledged that the planning and scoping phase of the exposure assessment is the optimal point to begin identifying vulnerable populations and lifestages, the document does not provide info on what criteria there is for determining if vulnerable populations or lifestages should be considered. It also does not provide information on who determines if this is an issue, what stakeholders need to be included, and what level of expertise should be required to ensure that these issues are incorporated appropriately. Perhaps incorporating "Executive Order 12898 Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations" would help better frame this discussion.

The organization of the chapter is confusing. Section 4.3 is supposed to provide examples of vulnerable populations and lifestages and Section 4.4 is on how to identify these groups. However, there is a sub-section of 4.3 that discusses "integrating age-specific values" in

exposure assessment. This doesn't really seem consistent with "examples". It may be good to have an additional subsection that discusses how to address vulnerable populations after they have been identified. Furthermore, there is a rather lengthy discussion on methods to identify regions of economic inequality in Section 4.3, which would seem more appropriate in Section 4.4.

This chapter needs more balance between the different vulnerable populations. For example, much detail is provided on children but the rest of the lifestages are lumped together. Similarly, there is quite a bit of detail on Native American tribes, but the rest of the races and ethnic groups are all grouped together in a very short section.

That being said the discussion on tribes is a very nice addition and should be commended. It tries to highlight cultural sensitivity that should be used and many other important considerations for conducting exposure assessments with tribes. In particular, there is a good discussion on the importance of the environment for Native American health and how for them the two go hand-in-hand. However, because of this close connection with their natural environment more emphasis should be placed on the fact that tribes are more likely to have more complete exposure pathways that need to be considered separately in an exposure assessment. It should also be emphasized that there are more than 500 federally recognized sovereign tribes and that they may have great differences in their cultural practices and beliefs and should not all be treated as the same. While this section is a great step forward, it needs to be reviewed by EPA's tribal partners and networks to make sure that it meets their needs and has appropriate cultural sensitivity.

The detailed discussion on inequality and the metrics is helpful, but can be shortened with references to the appropriate examples. It would also be important to discuss how to identify regions that are low-income. For example, is it possible for a region to have a low Gini because everyone is poor?

Assessment of social stressors is increasingly becoming an important part of cumulative risk assessment. It is great that this is acknowledged, but more guidance is needed on how to assess exposure to social stressors or at least more references related to the topic. Guidance on how to incorporate these (similar to the potency index for children) would also be helpful.

It needs to be emphasized throughout this Chapter that not only can vulnerable populations have increased exposures, but the way you assess exposures in these communities may need to different as well. This is particularly an important consideration for biomonitoring where certain groups may not be comfortable with providing biological samples because of cultural beliefs (e.g., hair, toenails, etc.) or because of previous misuse of samples (e.g., blood for genetic testing). These questions and discussions need to be handled with cultural sensitivity in order to maintain appropriate levels of trust in the problem formulation stage with these populations.

It is essential that exposure assessors review their conceptual model for the exposure assessment with the affected community to make sure that they are collecting the right samples to answer the question. For example, if there is concern regarding drinking water exposures it is essential to know if this is a population that drinks their tap water or bottled water. If you only sample tap

water, but no one drinks it, then you will not have an assessment of the drinking water exposure. Similarly, there may be additional exposure pathways unique to a "special populations" that need to be considered, such as the use of traditional folk remedies ('Greta') or makeup (e.g., henna or kohl) that may contain high levels of lead. Additional guidance on how to work with these populations to identify important yet unique exposure scenarios would be helpful.

Nicole Cardello Deziel, Ph.D., MHS

The addition of the chapter on vulnerable groups is a major step forward, and EPA should be commended for including this content. Adverse environmental exposures often occur in communities facing multiple social-economic stressors including deteriorating housing, inadequate access to health care, poor schools, and high unemployment, crime, and poverty – all of which may compound the risk of negative health effects.

This chapter could be improved in three areas: 1) terminology, 2) organization and consistent level of detail, and 3) better explanation of how to incorporate information on possible differential exposures among vulnerable subgroups into exposure estimates and risk assessments.

Terminology
Figure 4-1 does not align with the text and does not help illustrate the difference between vulnerability and susceptibility. The distinction between vulnerability and susceptibility was not clear. In particular, I think the most salient aspect of vulnerability for this document is differential exposures, and this concept needs a little more explanation and discussion of how to capture differential exposures in various subpopulations.

Organization and Consistent Level of Detail
The stated purpose of this chapter is to give an overview of vulnerable groups and help exposure assessors identify vulnerable groups. EPA could consider moving Section 4.4 up before Section 4.3 to say how one identifies groups and then give more detailed examples. In addition, I think it would be helpful to have a separate section on how to incorporate differential exposure estimates for vulnerable groups into the assessment.

Several pages are given to describe specifically how age-specific estimates can be calculated or how to work with tribal populations. I think it would be more effective to describe the broader principles of how to assess exposures among vulnerable subgroups and use these as examples. Many of the considerations mentioned have broader relevance to other groups.

Examples of other subgroups should receive some attention. For example, the emphasis of the section on children is on postnatal development. With increasing understanding about the developmental origins of disease hypothesis, it seems that some inclusion of the critical windows of fetal development should be included. How does EPA recommend that in utero exposures be estimated?

Research that aims to objectively quantify the socio-demographic features of communities and whether community disadvantage is associated with increased exposure is critical for improved

public health protection. With these findings, limited resources can be leveraged more efficiently to reduce exposure or mitigate health impacts for vulnerable populations. This chapter offers very detailed information about a few specific metrics for capturing income inequality. Other measures of social disadvantage are available, and it's not clear why EPA selected these. It would be clearer if a bigger picture view of these types of indices were presented with a table or chart of various available indices and their strengths or limitations would be better than having a lot of detail about a few specific metrics. For example, many environmental epidemiologists evaluate disadvantage indices using U.S. Census data on the demographic profile of the potentially impacted communities, including: age, sex, race/ethnicity, % population below poverty line, % population with high school degree and higher, education level, unemployment rate, homeowner status, median age of housing stock, per-capita income, and median household income.

Improved Explanation of How to Estimate Exposure to Vulnerable Subgroups
The chapter could be enhanced with improved clarity of how an exposure assessor would incorporate this sociodemographic information into an exposure assessment. Are there guidelines for how to integrate this? Are exposures just calculated for various subgroups? How would this be integrated with risk management? An additional section with a concrete example would be helpful.

Penelope A. Fenner-Crisp, Ph.D., DABT

I would give this chapter mixed reviews on the adequacy of the discussion on the topics covered. Sections 4.1, 4.2 and 4.3 are sufficiently detailed and provide references for those readers who have further inquiries. The reader can get some sense of what information the Agency considers to be of value and how they may use it.

I would recommend revision of the last sentence in the first paragraph of Section 4.3.2 Childhood on Page 44. EPA is NOT investigating ways to improve methods for conducting risk assessments for children solely in response to the Executive Order. Language in FQPA, SDWA and the new TSCA all mandate specific consideration of (sub)populations.

For instance, the new TSCA says
"In conducting a risk evaluation under this subsection, the Administrator shall—
(i) integrate and assess available information on hazards and exposures for the conditions of use of the chemical substance, including information that is relevant to specific risks of injury to health or the environment and information on *potentially exposed or susceptible subpopulations* (emphasis added) identified as relevant by the Administrator;
(ii) describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration;
(iii) not consider costs or other nonrisk factors;
(iv) take into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the conditions of use of the chemical substance ; and
(v) describe the weight of the scientific evidence for the identified hazard and exposure."

FQPA includes many special provisions for assessing risks to infants and children when setting tolerances for food-use pesticides and the 1996 amendments to SDWA speak to "…. the effect of such contaminants upon subgroups that comprise a meaningful portion of the general population (such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations) that are identifiable as being at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population."

The document states on Page 45 that "Information relating maternal exposure to chemical concentrations in breast milk, however, is sparse." Am I correct in assuming that the authors meant to say *infant* exposure rather than *maternal* exposure to breast milk, unless what is meant is "maternal exposures to chemicals found in breast milk?" If it is the former, there is a sizeable literature available on the presence of contaminants in breast milk, mostly persistent bioaccumulating substances such as the organochlorines insecticides (DDT/DDE, heptachlor etc.) and PCBs. If it is the latter, meaning the absence of literature which describes/measures/estimates of the levels of environmental exposure to the women which then resulted in specific levels in their milk, the sentence would be on point.

Are the resources cited in this section on Childhood currently relevant to the assessment practices of the Pesticide Program? In the past, OPP used different age groupings, different food consumption data and other factors than those presented in the Exposure Factors Handbook. I don't know if reconciliation ever occurred. If not, these Guidelines shouldn't give the false impression that all parts of the Agency are on the same page in this area.

The sections on Tribal Populations, Other Racial and Ethnic Populations and Socioeconomically Disadvantaged Populations are all rather lengthy and interesting for a variety of reasons, but they provide virtually no guidance on how to incorporate the information into an exposure assessment. Lots of discussion; little guidance and few resources cited which do provide direction. Can this be remedied? As an aside, it should be pointed out that there are always tribal representatives on several of EPA's stakeholder advisory groups such as the National Drinking Water Advisory Council (NDWAC), the Pesticide Program Dialogue Committee (OODC) and the National Environmental Justice Advisory Committee (NEJAC).

Section 4.4. Identifying Lifestages, Vulnerable Groups and Populations of Concern for Exposure Assessment is useful but would be much more so if each subsection were buttressed with more references, examples and guidance on how to use these methods/tools.

Christopher W. Greene, M.S.

Overall, I found this section to be well organized and effective at communicating the issues, with some exceptions as noted below.

I am concerned about some of the language used in the section on Native American tribes (4.3.5). Although unintentional, some readers might see Native Americans depicted as superstitious, anti-scientific people who "need to be made aware" of the issues. In my experience, tribal leaders and members are often very pro-science and forward thinking in their

attitudes towards environmental exposures, particularly in the areas of monitoring and green design. I think the authors know this, as evidenced by the excellent section on Resources for Assessing Exposures of Tribal populations (p. 50*ff*.) The text immediately preceding that section (p. 49-50) could use a rewrite with a wider perspective on Native American involvement with exposure assessment beyond merely being a population of concern. Would it be possible to get input on this whole section (4.3.5) from the EPA Tribal Network described on page 50?

I thought the section on age-specific values (4.3.4) was well done, but could be expanded to include exposure factors that vary with age and can be time-averaged in a manner similar to that described in the last sentence. For example, 95th percentile water intakes per unit body weight vary by about a factor of ten between infants and adults, and this may greatly influence exposure and risk management decisions, especially for acute and short-term exposures where the high intake rates of infancy make up the bulk of the exposure period. (Intake rates from EPA's Per Capita Water Consumption Report, see EPA-822-R-00-001) Moreover, these high intakes during infancy can affect risk decisions for long-term exposures as well: the difference in intake between infants and adults may exceed the difference (usually in the opposite direction) between toxicological reference doses for short-term and chronic exposure, so the long-term regulatory value may have to be reduced to be protective of the short-term, high-intake lifestage of infancy.

Numerous minor comments are provided in the table at the end of this document.

Michael A. Jayjock, Ph.D., CIH

I found this chapter to be very much like chapter 3 in that it is highly credible and educational, born of decades of solid EPA experience.

Although, I believe it is implied in this chapter, my sense is that there should be some explicit and reasonably pointed discussion about the need for matching exposure metrics and exposure durations with the same metrics and durations of the toxicological benchmarks used to evaluate and characterize risk. For example, acute exposures that occur in a time frame of minutes or hours need to be compared with toxicological benchmarks from experimental data over roughly the same time frame. Alternately, assumptions about or scaling of the toxicological benchmarks will be necessary and explicitly stated. As an example it would be inappropriate to compare a 1 hour inhalation exposure to a fast acting toxicant expressed in ppm concentration of the compound to an allowable daily (24 hour) exposure limit also expressed in ppm. In this case, some toxicological interpretation of the 24 hour limit would be required.

As a general principle, a differential in risk for any group comes from differences in toxic response per unit dose and/or inherent differences in levels of exposure for that group. This distinction should be made within the document with an example or two. Pregnant women's response to teratogens during the first trimester of pregnancy is an example of the first difference. Children's hand-to-mouth oral ingestion exposures versus that of adults represent an example of the second.

The data column on age-related potency adjustment in Table 4-2 indicates that it is specifically for cancer potency. The availability or lack thereof of other age-related potency adjustments

(e.g., acute –noncancer toxic potency, chronic – noncancer toxic potency) should be included and/or mentioned as a research need.

Rebecca T. Parkin, Ph.D., MPH

This chapter compiles insights and data obtained over the past 20 years. It offers the reader a good orientation to particular populations. There could be more said about pregnant women and their unique vulnerabilities related to the physiological changes of pregnancy. Mention of the unique aspects of fetal and elderly populations' exposures would also be appropriate.

The characteristics which distinguish "vulnerable groups" and "populations of concern" are not obvious as the chapter is currently structured and written. If this is an important distinction, modifications for clarity are needed.

Content: This chapter provides an effective discussion of lifestages, vulnerable groups and populations of concern. Examples and details offer the reader more routes to understand the importance of these populations in exposure assessment. Numerous statements in the chapter read as if they could be recommendations; these are useful to the reader. Some sections would benefit from clarifications or corrections.

"Vulnerability" and "susceptibility" are used in the introductory paragraphs of this chapter, but are not defined until two pages later. Perhaps parts of the paragraph at the bottom of p. 41 belongs in the introduction. The opening phrase of this paragraph ("Within the context of populations of concern,") is not necessary; the rest of the sentence could apply to all people. Because "susceptibility" is a component of "vulnerability," it does not need to be defined in the introduction of this chapter. The definition of "susceptibility" varies by discipline, (Parkin R and Balbus J, (October 2000), "Variations in Concepts of 'Susceptibility' in Risk Assessment." Risk Analysis. 20(5):603-620), however, so that the authors need to recognize that readers may approach this concept with very different contexts, altering their understanding of the issues presented in this chapter. It is important in this document to define terms, potentially across disciplines, to fit the specific needs of the exposure assessment process.

On p. 39 "vulnerability" is identified as "differential exposures," but more broadly described on pp. 41-43. It is not clear whether the statement on p. 39 is limited to EPA regulations and policies; clarification of this sentence would be helpful to the reader.

Section 4.4 provides practical guidance on and resources for identifying the populations discussed in this chapter. At the end of Section 4.4.1, the results of the "systematic review" would be of interest to the reader. The paper cited was not available online to discover and understand the outcomes of the review.

The second full paragraph on p. 60 does not have content related to exposure assessment. Although the data are interesting, this paragraph should be eliminated or modified to clarify the content's link to exposure assessment or deleted entirely.

Organization: The main organizational structure of this chapter is logical and clear, but the subsections within Section 4.3 are not obviously aligned with the title of that section. Sections 4.3.2 - 4.3.4 are, in fact, subsections of 4.3.1. It is not clear whether 4.3.5 (Tribal Populations) is the beginning of "vulnerable groups" or "populations of concern."

Presentation: Most of the extensive information presented in the text is clear; a few improvements are suggested (see III below). Most of the tables, figures and boxes are useful tools to enhance readers' comprehension of the text.

While interesting, the discussion of socioeconomic indices (section 4.3.7) is quite detailed and may be more than typical readers will want. If these are indices currently used by the Agency, then this section could be streamlined, referring the reader to an appendix for more information, examples and resources.

While a minor edit for Figure 4-2 is suggested in Section III, a more extensive discussion of Box 4-6 is appropriate here. The first line under the formula has a blank; this "X is _" should be x-bar for the mean, as shown in Fann et al (2011). The paragraph just above the figure is so close to the cited article that it should be modified (add in MP/RB) and put it in quotation marks to avoid the appearance of plagiarism. The status quo figure for asthma hospitalization risk was flagged in the original article as "greater inequality." Scanning the original article did not turn up the 2.241% shown on the figure. The mortality risk data shown were not age-standardized, but were used for sensitivity analysis. Upon further reflection, it may be determined that this Box is more than the intended reader needs and is not necessary to support the point made in the text about the "appealing" value of sensitivity analysis.

P. Barry Ryan, Ph.D.

As indicated, Chapter 4. Consideration of Lifestages, Vulnerable Groups and Populations of Concern in Exposure Assessments discusses the reasoning why selection of exposure lifestages is an important consideration in performing exposure studies. It starts with a historical background to the subject, lists a number of Executive Orders focusing on differential needs in specific populations, and follows this with a listing of USEPA's efforts in identifying its own resources in developing an understanding of disparities in exposure associated with age- and sub-population-specific exposure work (see Box 4-2, Page 41). Figure 4.1 (Page 42) gives a Venn diagram showing how differing factors can result in the likelihood of different impacts of what maybe identical exposures.

With the stage set, the Guidelines begin a discussion of specific lifestages and vulnerable groups that need special consideration in exposure assessment (Section 4.3). The last section deals with methods of selecting appropriate lifestages for exposure studies.

I have a few concerns with this Chapter. The organization is adequate for conveying the information, but I am not convinced that the structure is the best possible. For example, while of interest perhaps to policy makers, starting off the Chapter with a discussion of Executive Orders focusing on lifestages and vulnerable groups is of less use to the non-USEPA exposure scientists than it might be to the policy analyst. If one asks the question "have policy decisions been

helpful in producing information on this subject" then the emphasis on Executive Orders could be appropriate. However, few exposures studies are designed with this in mind. Most attempt to evaluate exposures to various stressors or agents and the outcome of such exposures. The discussion of lifestages and vulnerable populations should be of primary importance to these researchers. This was a point of discussion by others in the panel suggesting that modification of this section may be of use.

My second objection to the content and organization of this Chapter stems from giving essentially equal emphasis on Tribal Populations when compared to all others. USEPA has, of course, been a leader in looking at disparities in exposures experienced by Tribal Populations and this is reflected by the large number of reports focusing on such individuals (see Box 4-5.) However, there are many more children in the United States, approximately 125 million, when compared with the 5.2 million tribal members. Further, economically disadvantaged individuals, of which tribal members often are a part, is de-emphasized due to the focus on Tribal Populations. While many in Tribal Populations may be disadvantaged as well, I would expect that many more children are disadvantaged simply as a matter of numbers. I think the emphasis is misplaced in this Chapter. Children, including the developing fetus, are especially vulnerable to exposure to stressors or agents with potentially lifetime effects- and there are a lot of children. This is not to diminish the importance of understanding the special needs of Tribal Populations, but only to balance the coverage of populations based on their numbers and the likelihood of exposures being important.

I did bring up the codification of life stage categorization in the discussion at the meeting. I am still concerned that we, as a group of exposure scientists, have attempted to "carve in stone" the appropriate age groups of interest to exposure scientists. I think much more work must go into this area and each age group must be identified with respect to exposure and behavioral characteristics affecting their exposure and likely outcome prior to fixing on the specifics of the age-exposure-effect trichotomy. However, it may already be too late, alas.

Alan H. Stern, Dr.P.H., DABT

I have several problems with this section. "Vulnerability" and "susceptibility" are not well defined in the document. However, it is clear that the document uses "susceptibility" as a subset of "vulnerability." This is not (in my education and experience) a standard use of these terms. This deserves more discussion. While the concepts of vulnerability and susceptibility are clearly important determinants in public health outcome, this section does not make clear how these concepts are to be integrated into exposure assessment. Whether or not a receptor population is more at risk because of economic, racial, or other social factors, the pathways of exposure should be the same. If key exposure factors differ because of these factors, that should be addressed in terms of the appropriate exposure factors. If this section is intended to set forth an EPA policy regarding the role of socioeconomic factors in exposure assessment, that should be clearly spelled out and methods for integrating those factors into the exposure assessment should be discussed. As it currently stands, the document does not address issues of this integration.

As stated in my previous comments, the several indexes described in this section have not traditionally been part of exposure assessment, and exposure scientists may not have been trained in their use or application. Given this, the level of detail is too great if the intent is to merely provide a link to specific and detailed information on their use and application, and not detailed enough to allow an exposure assessor to us them based on the information provided.

On pg. 41, neither of the definitions of vulnerability or susceptibility clearly addresses behavior patterns/time-activity patterns that can lead to increased exposure. This is a major consideration and it is not clear from these definitions whether this falls under vulnerability or susceptibility.

The explanation of the Atkinson index in the last paragraph on pg. 54 is not intuitive or clear.

The example of the use of the Atkinson index in the box on pg. 56 is confusing. The example seems to imply that the Atkinson index was used to show that one particular pollution control strategy was more effective in reducing disparities in risk from PM 2.5. Presumably, populations with greater socioeconomic disparities are more vulnerable to health effects from PM 2.5, and the particular PM 2.5 strategy was more effective in reducing their exposure. However, it is not clear how choosing a more effective control strategy relates to exposure assessment.

In section 4.4.4, it is stated, with respect to population-based methods that, "This comparison requires data on each person in a population." Why is that the case? This appears to be unnecessarily burdensome and unnecessarily data rich compared to the use of a statistical valid sample of the population.

The third paragraph on pg. 60 presents the number of cases of diagnosed pesticide poisonings each year among migrant farm workers as an example of a "national-level assessment." How is this an example of an exposure assessment?

Clifford P. Weisel, Ph.D.

The chapter is organized to describe three broad population groups of concern identified in Presidential Executive Orders: Children, Tribal Groups and Environmental Justice Populations. This chapter includes a description of how to conduct population based exposure characterization, particularly as they may apply to those groups. While this approach does not provide a completely smooth transition within the chapter it does allow the key information be presented to meet the Agency's directive. Suggest that the chapter starts with the basic premise of understanding how lifestages and being members of vulnerable groups and populations can affect exposure – do use an adult, urban, middle class male as the model for all exposure assessment but recognize the traits of the representative individuals in the study population. Following, lay out some of the key lifestages and vulnerable population and then introduce the populations that will be used as an example on how some of the issues related to exposure assessment in those population.

Two lifestages that are mentioned but not adequately addressed in this chapter are: pregnant women/fetus and the elderly. Their lifestyles and behavioral activities can differ from other age groups resulting in differing exposures.

The chapter does discuss how exposure, and not just inherent susceptibility, varies across these groups, which is an important consideration for developing an exposure characterization. Examples provided were: not only do children have higher breathing rates and ingest more food by kg than adults (which is well known) but are closer to the ground so breathe different air which may not have been recognized, but is a consideration in exposure; and that subsistent fishing that occurs for some tribal populations leads to much higher exposure to contaminants present in some fish. Figure 4-2 shows different behavior patterns with age and is useful for a novice doing his or her first exposure assessment for children.

A discussion is provided on approaches to recruit and work with Tribal groups, followed by a discussion of considerations of other racial and ethnic populations. The discussions emphasize that these interactions require understanding the culture of each group, which is appropriate. There may have been too much emphasis on tribal study considerations as a specific populations rather than an example of what might need to be considered. Less guidance was provided to working with children which also has a number of unique considerations and is a larger population.

There is a discussion on identifying economic inequalities on a population basis though the chapter did not elucidate what exposure differences might result on either a community/ environmental bases (e.g., prevalence of industry, manufacturing, traffic in a community) or for individual households (e.g., indoor air differences for residents and other locations frequented, dietary differences, smoking differences). A few sentences to guide individuals as what type of difference to consider would be helpful. The role that economic differences may play in social stressors, which is linked to exposure and health, is addressed. I suggest expanding the discussion on the relationship between Geographic Location and Environmental Justice.

Section 4.4 outlines the basic approaches to exposure characterizations for populations and identifies a number of data bases or tools that can be used. However, this section does not build on the earlier discussions of incorporating community groups to understand the culture and location specific issues that can lead to environmental exposures. I would have expected this to be more forcefully discussed in the final section on Local-Level Assessment, rather than the passive language used of "responding to specific community concerns". It should restate the importance of working with community to identify their concerns early in the process and understanding the culture and community to develop a valid risk assessment and risk management plan.

Chapter 5. Data for Exposure Assessment - discusses data used for exposure assessments, including determining what data are needed; whether data are currently available and the quality of the available data; and when data are not available, whether the data should be developed to meet the needs of the project. Guidance on the assessment of data uncertainty and variability is also presented in this chapter.

Question 5. Please comment on this chapter's discussion of the selection, assessment, and use of data in exposure assessments.

Paloma Beamer, Ph.D.

Chapter 5 is a very ambitious chapter that covers everything from the use of existing data sources in exposure assessment through designing and conducting an observational exposure study. This Chapter is very well organized and remarkably comprehensive given the breadth that it covers.

Addressing what to do with non-detectable values is extremely important in exposure assessment and I am glad to see that this section is included. However, I think the section could benefit from providing additional guidelines. What are the current recommendations for simple substitution methods? Which ones are preferred and for which scenarios? If an analyte is detected but not above the minimum quantification limit is it better to do a simple substitution for all values or use the detected values? Why or why not? Many times in exposure assessment to be consistent with NHANES, non-detectable values are substituted with the LOD divided by the square root of 2 (Hornung et al., 1990). The treatment of censored values can change the conclusions of an exposure assessment. Therefore, more clearly articulated guidance is needed perhaps similar to that in the book: *A Strategy for Assessing and Managing Occupational Exposures* (Jahn et al., 2015).

Decisions regarding how to deal with censored data may also differ by the purpose of the exposure assessment and between modeling or measurement studies. For example, if the purpose is to characterize the overall distribution of exposure following an observational study, it may be appropriate to just report various percentiles as ND (non-detectable). It is also important to highlight that values below the LOD can still be sampled using probabilistic techniques as part of a modeling study.

Exposure distributions are often log-normal because environmental concentrations are log-normally distributed (Ott, WR (1990) "A physical explanation of the lognormality of pollutant concentrations, J AWMA, 40:10, 1378-1383). Thus, many times exposure distributions are reported with the geometric mean and geometric standard deviation. It would be appropriate to add the GM as an appropriate method to describe the central tendency of an exposure distribution. May want to consider a discussion as to when the geometric mean would be preferred over the arithmetic mean. A good discussion is also provided in the book: *A Strategy for Assessing and Managing Occupational Exposures* (Jahn et al., 2015). At the very least recommendations on assessing the distribution of the exposure assessment results and how that impacts the appropriate summary statistics should be provided.

There is a very nice discussion of questions to ask when considering/evaluating exposure data (Table 5-2). It would be useful to have a list of considerations or examples that should be taken into account when evaluating when different data sets for prioritization or when assessors are considering combining different data sets, such as making sure all the data sets you are using for concentrations in soil utilized comparable methods. While this is the point of this section, it may be useful to have specific examples (e.g., same sieve size used? same acid used for digestion?) and describe why this may affect the exposure assessment.

Very nice discussion of considerations related to the collection of biomonitoring data. Here are an additional few topics that warrant consideration prior to conducting a biomonitoring study, and should be added as bullet points in Section 5.4.3. First, are there appropriate reference levels to make the results meaningful to the target population? Or will you measure a contaminant in biological media for the first time, and therefore not be able to inform the participants if these levels are high or not? Second, are there other measurements that need to be taken to normalize the results between participants such as creatinine in urine or lipids in breast milk? Typically if you address question #1, this will help identify the answer for question #2. It is important to take this into consideration at the onset in case the samples need to be collected, treated or analyzed differently.

Table 5-6 lists an impressive and comprehensive list of existing data for exposure assessment. However, it is not readily clear which of these datasets are still on-going and longitudinal assessments and which are cross-sectional and completed one-time assessments. It would also be helpful to have a column for the time period corresponding to the study (i.e., the years the study was conducted). Some of these studies are important resources, but users should realize they may be over 20 years old, and not necessarily representative of current populations. It would also be helpful to include the location for those studies conducted on a local or state level so that one can readily determine if it would be representative of the current community being assessed.

Because this document is likely to be read by individuals outside EPA, it would be helpful to have citations to "exposure point concentrations" and the appropriate legislative mandates. At the very least, guidance on determining the appropriate legislative mandates for an exposure scenario or links to resources to aid you in that should be added. It would also be helpful to have some relevant examples, even if it needs to be emphasized that these are not exhaustive lists.

This Chapter provides an excellent opportunity for discussion of how existing measurement studies and exposure modeling can be used together to answer important questions such as contributions of routes of exposure, or for model evaluation. It could also be emphasized that analysis of existing data sets or model estimates can be used to inform future observational study designs.

Hornung RW, Reed LD. Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 1990;5(1):46-51.

Nicole Cardello Deziel, Ph.D., MHS

This is an important and useful chapter with a clear presentation and a lot of information. I like the tables and the format of section 5.4 with the posing of questions to illustrate importance concepts. I think the questions are important and the guiding principles have an appropriate amount of specificity while recognizing the need for flexibility depending on the available data. Exposure assessors can use these questions to methodically evaluate the data quality.

P. 67- "The use of low-quality data in an exposure assessment is possible if the limitations in the data can be demonstrated not to affect the results significantly." I think this should be followed with some specific suggestions, such as sensitivity analyses or simulations can be used to see if similar conclusions are reached under different scenarios or assumptions.

This chapter would be strengthened with the inclusion of some discussion of the temporal variability in environmental and biological measures and an evaluation of how representative is a single sample or issues of seasonality of exposures. It could discuss various exposure profiles and could offer some parameters for capturing the repeatability of a measure, such as the intra-class correlation coefficient.

The chapter recognizes that publically available literature may serve as a rich resource, but does not provide any resources to assist with a literature review. A link to the EPA HERO database would be helpful, as well as potentially PubMed or Web of Science.

Penelope A. Fenner-Crisp, Ph.D., DABT

In my view, this is the first chapter that provides a useful level of detail on the topics covered. The reader can get a sense of what's known and how one might go about using the information and resources cited---with one exception. Implicit in the discussion is that the exposure assessor has access to the *raw data* from all of the available studies and would also have access to raw data from any new Agency-commissioned study conducted to fill in critical data gaps. In this case, s/he can do all the necessary independent evaluation, validation, QA, integration, etc. That is likely possible with studies conducted by EPA or another government agency. It's NOT likely the case with studies published in the peer-reviewed literature. I think it would be important for the Agency to address this issue in these guidelines by articulating a policy on how it would deal with studies for which the raw data are not made available to the Agency.

Also, there should some discussion of how one would conduct a weight-of-the-evidence evaluation of multiple datasets, particularly those of differing quality.

And, there should be discussion of "Stopping rules," that is, "When is enough, enough?" The goal should be having just enough information to make credible decisions, and not continue to collect data beyond that point.

The figure depicting a Conceptual Model introduced in Chapter 3, Section 3.2.2 should be reprised here.

Section 5.2.2-Addressing non-detect values----It might be useful to provide an example/case study. A brief description of OPP's approach for dealing with this issue would serve. It is described in OPP. 2000. Assigning Values to Nondetected/Nonquantified Pesticide Residues in Human Health Food Exposure Assessments.
https://archive.epa.gov/pesticides/trac/web/pdf/trac3b012.pdf.

Section 5.4.5 Questionnaires, Surveys and Observations
This section is one of several places where the Guidelines refer to the Agency's DQO process, "…a systematic planning tool, based on the scientific method, for establishing criteria for data quality and developing data collection designs." How will the DQO process meld/blend with the forthcoming Systematic Review policies and practices?

Section 5.6 Data Management

This section speaks to the issue of release of privacy or proprietary data to the public. As noted, there are legal and other constraints on releasing and sharing certain categories of information between and among parties of many stripes. This constraint even applies between government bodies (e.g., EPA currently does not have access to ECHA's REACH profiles). Lack of access can be a two-way street. It can prevent the Agency from accessing raw data for evaluation and integration into an assessment and it can hamper the ability of outside parties to critique and/or replicate an assessment that the Agency has in progress or completed.

There are, however, options available which would allow access to raw data while protecting proprietary information, participant confidentiality and the intellectual property rights of researchers.

With regard to papers published in the peer-reviewed literature, generally, there is a lack of access to sufficient information for the reader to attempt a replication of the assessment or research study. A growing number of journals now allow authors to provide supplementary information with their manuscripts. A smaller number are fully open access and invite the authors to upload all of the details of methods used and results gathered. Further improvements in the publishing arena are forthcoming as a result of the issuance of the Principles and Guidelines for Reporting Preclinical Research, which were agreed upon in a gathering of more than 30 major journal editors, representatives from funding agencies, and scientific leaders that was convened by NIH and the journals *Nature* and *Science* (NIH. 2015. Principles and Guidelines for Reporting Preclinical Research. Bethesda, MD. Available at: http://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research).

Models for sharing sensitive or proprietary data with third parties are available (e.g., Khan K, Weeks A. 2016. Dryad in the UK and USA - prospective and retrospective data publication. Toxicol. Sci. Advance Access. First published online July 27, 2016. doi:10.1093/toxsci/kfw132).

On occasion, OPP grants access to Confidential Business Information (CBI) to FIFRA Scientific Advisory Panel members when preparing for, and participating in, an SAP meeting on a specific

topic. The Panel members are held to the same standards and consequences as are the Program staff.

Access also could be granted to an independent outside party for independent analyses under strict confidentiality agreements and with data protection. This was done for the Health Effects Institute's reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality (HEI (Health Effects Institute) 2000. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. July 2000. Available at: https://www.healtheffects.org/publications).

The Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics has a policy on granting access to nonpublic use of NHANES data (CDC. 2015. Guidance on Granting Access to Nonpublic Use of NCHS Data. February 2015. Available at: https://www.cdc.gov/nchs/data/nhanes/nhanes_release_policy.pdf)

Christopher W. Greene, M.S.

This chapter contains a lot of useful information, but I found it a little hard to follow at times. It may be helpful to put the "types of data" section (5.3) at the beginning, because it clearly lays out the major types of exposure assessment data. This could then be followed with the sections that advise the reader on how to plan and execute the assessment. This chapter covers two different exposure assessment processes: exposure assessments using existing data, and the design and execution of projects to generate new data on exposure. Sometimes it is not clear which of these two processes are being discussed in any given part of the chapter.

This chapter would also benefit from the inclusion of consumer product data and food data under the "types of data" section (5.3.) It seems like these two data types could be discussed under section 5.3.4 on Observational Human Exposure Measurement Study Data, but as currently written, they may not fit under that definition. The document could also provide resources for finding data on chemicals in consumer products and food.

Other, more minor comments on this chapter are provided in the table at the end of thiss document.

Michael A. Jayjock, Ph.D., CIH

I found two broken links in Table 5-6 which is in general an outstanding resource for exposure assessor. These were links in which I have a particular interest as an exposure assessor. I suggest checking all of the links in this table and the rest of the guidelines document.

I agree with Dr. Beamer that specific advice on handling non-detect samples from monitoring should be included. I also agree with Mr. Greene that included in this discussion should be the need to choose a method with a detection level that provides useful information relative to the toxicological benchmarks being used for the chemical(s) of interest.

This chapter is rich and fairly comprehensive in its coverage of general data needs for exposure assessment. There is, however, one area that I suggest should have received greater coverage within this chapter that, in my opinion, did not receive enough attention. The second sentence in this chapter is:

> Possible data types include physical measurements of environmental and biological media, health survey and study outputs, location-specific or population-based activity information and **scientific research findings**. (emphasis added)

The term "scientific research findings" could be viewed as a catch all to include model input parameters. From my perspective, these data are critical to the proper use of models for exposure assessment. They are critical in lowering uncertainty and elevating confidence in that any and all models rely on reasonably accurate input into order to provide credible exposure predictions.

Examples of critical parameters included:

- evaporation rate of solvents
- emission rates from residential building materials and other items or activities used or occurring indoors
- air velocity indoors
- eddy diffusion indoors and outdoors in nearfield microenvironments
- fresh and interzonal air exchange rates indoors (residential and industrial)

A series of workshops on exposure modeling was held in Italy in 2006 under the auspices of the European Commission. A broad base of exposure assessment experts world-wide attended with representation from the EPA and the academic community. A report with specific recommendations on nearfield exposure source research needs was generated during that meeting (European Commission, 2006: Global Net on "CONSUMER EXPOSURE MODELLING" Report of the Workshop no. 2 on Source Characterization, Transport and Fate. Directorate-General Joint Research Centre Institute for Health and Consumer Protection (available on request from mjayjock@gmail.com).

Some discussion of this topic, its critical importance and the need for these model input parameters would be a valuable addition to the guidelines.

On a related matter, the EPA has lead the world in the development of what might be termed "sub" models; namely, physical-chemical models or databases that can provide the input parameters for larger/ higher level exposure models. Some examples include iSVOC, Params and MCCEM. These models used to be available for download from the Agency; however, they presented problems in that they would only run on PCs with older operating systems. Reportedly, a project is underway within the Agency to collect and incorporate these into one website and make them executable as web-based programs. Some discussion should be in the guidelines as to the status of this effort and the projected date for its completion. In the meantime, all of these PC-based programs should be made available again on an EPA web site with the qualification that they will only work in earlier versions of Windows (*e.g.,* XP) or

alternatively as Window XP in a freely available virtual PC application (*e.g.*, Oracle VM Virtual Box).

Rebecca T. Parkin, Ph.D., MPH

This chapter provides effective descriptions of data-related issues and offers sound advice and recommendations. The text implies a series of steps for assessors to consider. The figures, tables and boxes offer consistent and substantive support to the text; some (e.g., Figure 5-1 and Table 5-1) work together, offering the reader two ways to understand the concepts presented.

Points about data selection, assessment and use are found throughout the chapter; the first two topics are primarily in Sections 5.1-5.4 and use is predominantly in Sections 5.3-5.7. The following comments are synthesized across relevant sections.

Selection: The authors correctly note that an assessor should begin the process of selecting data by ensuring that he/she understands the conceptual model and can frame relevant exposure scenarios. Understanding the objective of the study is another fundamental element in selecting data. Additionally, the issue raised earlier about having a clear question or hypothesis which guides the assessment would be appropriate here as well. If that concern is fully discussed in Chapter 3, however, a cross-reference here would be sufficient.

The authors indicate that only after the assessor recognizes the correct time and location parameters, the populations of concern, and the likely routes of exposure can he/she proceed to determine whether 1) data already exist that would meet the study's purpose and be representative of the population or 2) a sampling program would be necessary. Even if existing data are suitable, the authors advise assessors to consider whether there are gaps in those data which could be filled with new samples. Furthermore, are there special issues (e.g., access, confidentiality, etc.) which may limit the anticipated use of the data? After addressing these issues, the assessors may have to reconsider the question or hypothesis driving the assessment. If data and modeling cannot adequately address the question/hypothesis, should the assessment continue with a revised foundation or be stopped with a clear discussion as to why the work did not proceed? The potential for returning to the fundamental question/hypothesis is not acknowledged.

Various types of data are described, including environmental samples, biomonitoring results, and observational and self-reported data. The authors comment on key challenges, strengths, weaknesses and the utility of each type of data for exposure assessment purposes. They also point out important issues for exposure assessors to address before proceeding. But handling non-detects and the context of limits of detection are not adequately considered in the discussion.

Assessment: The text describes many elements to consider when determining whether an existing data base is sufficient for study purposes or whether new data are required. The assessment of data is one of the most extensive discussions in the document. This emphasis is merited given the pivotal role of data in exposure assessment processes.

For existing data, knowing the methods and procedures used, the key uncertainties in the study and data, the defaults and assumptions used, the compliance of the dataset with EPA requirements (such as DQO, QA/QC and QAPP), etc., will aid the assessor in defining the fundamental characteristics and thereby the utility of the data base. Addressing all of these concerns will increase the effectiveness of exposure assessors' data evaluation processes and decisions. Raw data may not be readily accessible, however, for a variety of reasons. In some cases, knowing background or reference levels is necessary to interpret the field data. This point was not found in the draft guidelines.

If acceptable data do not exist, the assessor must determine, for example, whether a sampling program would be feasible and timely, whether it would meet the study objectives, whether enough data could be collected for meaningful use in an exposure assessment, whether the data would meet EPA's five data quality factors (Section 5.2), whether they would meet both performance and acceptance criteria, etc.

The bottom of p. 80 (Section 5.4.1) presents a question which refers to space and time. Although the following sentences discuss the spatial dimension, time is not addressed. This omission should be corrected.

The sources of data uncertainty are discussed in Section 5.5. In the first bullet on p. 91, the example suggests that "A higher confidence rating" for a factor relates to less uncertainty. While this is true, it is too simple to leave the impression with the reader that this may be the only factor that determined a high rating. Many factors were used (see EPA, 2011f, pp. 1-5 through 1-7) and should be at least noted here. The reader should leave this section understanding that uncertainty is driven by a complex relationship of many factors.

Use: Most of the text relevant to the use of data in exposure assessment is toward the end of the chapter. The authors note that the assessor must know whether the data quality will or will not substantially affect the outcome; expert evaluation of uncertainty is very important to the assessor's understanding. The authors also point out the value of addressing nondetects, examining outliers for insights, using bounding estimates and exposure point concentrations, and characterizing exposure estimates effectively. Data management issues in this chapter include QA/QC, FOIA and other key topics. Aspects of external data communications are considered and recommendations are made in the final section of this chapter. The text discusses modeling issues, while referring the reader to the next chapter, focused on exposure assessment models.

P. Barry Ryan, Ph.D.

This Chapter is quite essentially based on the USEPA concept of Data Quality Objectives (DQOs) and is focused on collecting exposure data sufficient to produce high quality and useful data. The components are defined in the bulleted list on page 64 and schematically displayed using different terms in Figure 5-2. Box 5-1 references several USEPA documents and webpages that aid the reader in understanding the DQO process.

The essential task at hand is to produce exposure data commensurate with "… the degree of uncertainty the project team is willing to accept based on the needs of the risk manager/decision

maker." (See page 67). The document discusses several possible ways of developing quality data and discusses what such data might look like in a hypothetical sense. Further it addresses data quality issues and how data currently extant may be used to improve a design. The Chapter focuses on both environmental data, biomonitoring data, and exposure factors as mechanisms for understand the exposures experienced by individuals in a study and urges researchers to evaluate what such exposures might be- at least to bound them- prior to beginning data collection. It also addresses issues of uncertainty and variability, distinguishing between them.

This Chapter gets back to the operational method of pointing out definitions, methods, and approach to be considered in the collection of environmental and biological exposure data and away from advising on who should be monitored. I think it is stronger for this focus and adequately designed and implemented. The examples are useful. They are not meant to be concrete or specific in any fashion, but rather provide examples and pathways to quality data. Finally, the Chapter presents in tabular form descriptions and access to a large number of exposure studies completed for which data and descriptions exist.

The Chapter is quite long, spanning over 40 pages. At times it becomes somewhat unwieldy. It may be strengthened through editing for length and content. The sections on DQOs becomes somewhat pedantic at times and could truly benefit from some tightening. However, overall this is a good overview that should be read and digested by essentially all exposure scientists and especially those contemplating their first study design.

Despite my concerns about length, I can offer no real good method for shortening. It might be necessary to re-write the chapter from scratch with an eye toward conciseness and clarity with only essential aspects discussed. As a complete alternative, the chapter may be extended with much more detail presented and then published as a separate monograph. This monograph would then be referenced by these guidelines.

Alan H. Stern, Dr.P.H., DABT

As discussed previously for some of the concepts in this chapter, particularly biomonitoring, the level of technical detail is either too much (for an introductory survey), or too little (for technical guidance).

In Table 5-1, the exposure points for "soil" are given as residential yards, and on-site. Contaminates soil can also enter the indoor environment and result in exposure by all routes. If indoor soil exposure was intentionally omitted because indoor soil is considered dust, then a separate category should be created in the table for dust.

The second paragraph on pg. 75 is a good and important caveat.

Section 5.2.2 deals with methods for dealing with non-detect samples. However, it is critical to address the *selection* of analytical methods that are fit-to-purpose so as to minimize non-detect samples in the range of interest.

In box 5-2, the definitions of "high end distribution" and maximum exposure range need to be

more fleshed out, and the arbitrariness of these terms needs to be given more discussion. Also, "maximum exposure range" is particularly ill-defined and something of an oxymoron since the "maximum" must be a point and not a range.

In Table 5-3, the distinction between the categories of "microenvironmental sampling" and "personal monitoring" is blurred when it comes to air monitoring.

In the first paragraph on pg. 85, it should be noted that biomonitoring data *can* provide strong evidence for a specific source if the chemical in question is rare in the general environment. Also, the document should note that while biomonitoring is often weak in identifying specific sources of exposure (but strong in identifying and quantifying internal exposure), sampling of environmental media is often weak in quantifying internal exposure (but strong in identifying sources of exposure). The use of the two methods together, however, can be particularly powerful in linking sources and internal exposures. Examples of this can be found in:

> Stern, A.H.; Fagliano, J.A.; Savrin, J.E.; Freeman, N.C.G.; and Lioy P.J. The Association of Chromium in Household Dust with Urinary Chromium in Residences Adjacent to Chromate Waste Sites. Environmental Health Perspectives 106:833-839 (1998).
>
> Stern AH, Gochfeld M, Lioy PJ. Two decades of exposure assessment studies on chromate production waste in Jersey City, New Jersey-what we have learned about exposure characterization and its value to public health and remediation. J Expo Sci Environ Epidemiol. 2013 Jan-Feb;23(1):2-12. doi: 10.1038/jes.2012.100. Epub 2012 Nov 7.

On pg. 88, in the fifth bullet, if the activity records are kept by the person under evaluation, how do such studies differ from "respondent estimates" or "diaries?"

Section 5-7, "Data Communication" should be expanded to include outreach, public meetings, etc.

Clifford P. Weisel, Ph.D.

I would suggest that a broader list of sources, pathways and routes of exposure be provided before the conceptual model for the release of chemicals from a drum is used as an illustration, since the conceptual model for the release of chemicals from a drum is not all inclusive. The indoor air and indoor sources, which for most individuals is the major exposure pathway for indoor exposures to both volatile compounds and many particulates for most individuals is underrepresented in the proposed scenario. Similarly, soil contact in playground is not included for children, nor is household dust. Household dust should be incorporated in several places in this chapter and text as major repository for many toxics that adults and particularly, children, can be exposed to.

Consistent with the Agency's policy, there is a strong section on the need for Data Quality Objects, a Quality Assurance Project Plan and QA/QC protocols. While I appreciate the need to

deal with non-detect values and outlier data, this could be accomplished by referencing standard EPA procedures for handling these rather than a full page of detailed procedures. This level of explanation and details is needed for biomonitoring and exposure factors since this is more likely to be new to EPA personnel using the guideline as their initial foray into exposure assessment. It would be beneficial to elaborate on how people's physical characteristics are exposure factors (last sentence page 75).

Page 80, paragraph entitled "Were the data collected close to an exposure point of concern in space and time", describes why measurements need to be made where the people are. However, a similar description of the time factor is not included. Since people activities can greatly alter the exposure with time to not only the person involved in the activity but also to others around him or her, temporal components of exposure should also be highlighted, particularly for acute exposures.

This chapter should highlight data for both aggregate and cumulative exposures; the need to consider multi-chemical, multi-route, and multi-pathway exposures; and data available and the importance of considering non-chemical stressors, concepts introduced in the background chapter.

Table 5.3 needs work. My problems with the table include the following:

The rationale for the categories is not obvious and what is provided may be too constricting. While the table is expected to be used as the starting point it is far from comprehensive and may not be sufficiently informative for the reader. Some deficiencies, based on the Type of Measurement provided, are:

Fixed location media monitors – Target media does not include dust, Examples are for water and air but not for soil, sediment (note: sediment is not a common media that people are exposed to) or dust. The examples are extremely generic.

Short-term media monitoring - enclosed environment and transportation is not included. Does RCRA really deal with short term monitoring?

Source monitoring – the two categories: air and waste streams, are at different levels of specificity. Water treatment plants and distribution systems and mobile source emissions are missing for existing data.

Consumer product sampling - consumer product data base should be listed for existing data.

Microenvironmental sampling – media should specify indoor air (list: residences, offices, commercial establishments, recreational) and maybe ambient air; swimming pool water

Personal monitoring –under media - why is ambient air and indoor air listed and not personal or breathing zone air? Include duplicate plate for food.

Chapter 6. Computational Modeling for Exposure Assessment - highlights concepts in modeling, including the principles of the modeling process. It provides an overview of modeling for exposure assessment, outlines the criteria for choosing appropriate models based on the goals and data quality objectives and describes how to evaluate a model that might be useful for an exposure assessment. Chapter 6 also includes information on modeling inventories and clearinghouses, and resources that support the use of models of various levels of complexity.

Question 6. Please comment on the presentation of issues related to selection and use of exposure models.

Paloma Beamer, Ph.D.

Traditional risk assessors are very hesitant to use computational modeling. Chapter 6 does a very nice job of laying out the steps and why it is important to consider using more complicated models. Hopefully, this Chapter will help us move past the simplified "worst-case" scenario approaches to at least consider sensitivity analyses on the assumptions made.

In particular, the authors did a very good job of emphasizing that model development and evaluation is a multifaceted activity that requires input from stakeholders and real data. They also laid out the importance of critically evaluating existing models for purposes other than those for which they were initially designed.

What would be useful is additional guidance on defining "worst-case" scenarios. How should "worst-case" scenarios be defined and from whose perspective? Many times regional assessments may conduct a "worst-case" exposure scenario but it only incorporates one exposure pathway when in fact there may be many for which the public has concerns. This can make the public feel like risk assessors are cherry-picking the one exposure scenario and their assumptions so that there is no risk. In a recent risk assessment involving multiple state and federal agencies different exposure scenarios were used by each agency, resulting in 3 orders of magnitude difference in screening values. This is very confusing for the public to understand. Guidance on a more transparent process with public input would be helpful, particularly for those scenarios when a more complicated and detailed assessment is not warranted.

It should be emphasized that worst-case scenarios should also consider aggregate exposures via multiple routes and cumulative exposures to multiple chemicals. Just because one exposure pathway for one chemical results in a estimate below a screening value, even when using very conservative assumptions, this does not mean this would be true if multiple pathways were considered or for multiple chemicals simultaneously.

It would be good to emphasize that PBPK models require special consideration for children. Many times, children are simply treated like miniature adults and the tissue volumes and perfusion rates are scaled as a function of body weight and height. However, this is not the case. It is important that modelers consider each parameter in the PBPK model and determine how it may be altered for the current lifestage being assessed. Here are examples of parameters that may be altered: protein binding of lipophilic compounds, water/lipid composition of body

tissues, urinary clearance rate, enzyme kinetics, and creatinine excretion. We demonstrated this successfully in a PBPK model we developed and successfully evaluated for children (Beamer et al., 2012). Other groups who did not take into account all of these factors or key exposure routes were not able to successfully evaluate their models (Lu et al., 2010).

Beamer PI, Canales RA, Ferguson AC, Leckie JO, Bradman A. Relative pesticide and exposure route contribution to aggregate and cumulative dose in young farmworker children. International Journal of Environmental Research and Public Health 2012;9(1):73-96.

Lu C, Holbrook CM, Andres LM. The Implications of Using a Physiologically Based Pharmacokinetic (PBPK) Model for Pesticide Risk Assessment. Environ Health Perspect 2010;118(1):125-130.

It should be emphasized more throughout that the most parsimonious or simplest model that fits the exposure assessment need should be used. While a more complicated model may be developed if there is not enough information regarding the additional input parameters this may just create additional unnecessary uncertainty in the exposure estimates. In essence, models should not be more complicated than they need to be to answer the pertinent question.

Guidance needs to be provided on model verification and evaluation. Additional guidance should be provided on what to do in scenarios when there is no measurement data to evaluate the model with.

Nicole Cardello Deziel, Ph.D., MHS

This chapter provides numerous resources for identifying and selecting the appropriate model for a given assessment. It provides information on models of varying levels of complexity. The fate and transport section could include some discussion of simple inverse-distance-weighted models, land-use regression models, and simple dispersion models. I agree with comments made by other panelists that a statement that the most parsimonious model that appropriately fits the exposure assessment need should be used.

Penelope A. Fenner-Crisp, Ph.D., DABT

This chapter reflects a balanced presentation of the issues—not too sparse, not too detailed. I have no suggestions for modifications.

This chapter shows the value of briefly citing a few case studies and citing resources which contain them such as U.S. EPA. 2014d. Risk Assessment Forum White Paper: Probabilistic Risk Assessment Methods and Case Studies. (EPA/100/R-14/004) or U.S. EPA 2001g, Appendix D of Risk Assessment Guidance for Superfund: Volume III – Part A, Process for Conducting Probabilistic Risk Assessment.

Another resource that might be useful to add to Table 6-1, even though it is not EPA-generated, is OECD 2012. Descriptions of Existing Models and Tools Used for Exposure Assessment. Results of OECD Survey Series on Testing and Assessment No. 182. ENV/JM/MONO(2012)37.

Available at: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2012)37&doclanguage=en

Section 6.2. Selecting the Type of Model for Exposure Assessments might be a good location to speak to the need for the assessor to provide the justification for his/her selection of the model(s) s/he is using in a particular exposure assessment.

Christopher W. Greene, M.S.

I would think that in addition to the sections on modeling principles and model selection (6.1 and 6.2), what the reader really wants out of this chapter is a good list of models, what they are useful for (their "tier," inputs, and outputs,) and where to acquire more information. Chapter 5 ended with a long list of data sources; why not include a big table of models in this chapter? I think this would be more effective than the approach as currently written, where models are referenced in the text, making it harder to compare models to one another. Such a table would add value to the Guidelines document, providing users an organized inventory of models commonly used in exposure assessment. Table 6-1 is a good starting point, but could be greatly expanded.

That said, I found this chapter to be concise and well-organized into three neat sections. I appreciated the provision of examples in key places (such as Table 6-2.) As in other parts of the Guidelines, some of the figures need further explanation, especially Figure 6-3.

Additional comments are provided in the table at the end of the document.

Michael A. Jayjock, Ph.D., CIH

In general the chapter properly identifies and does a good job of explaining most of the issues that I can think of relating to the selection and use of exposure models with an exception noted below.

The current chapter lists 4 categories of models; namely:

- Fate and transport
- Integrated fate/transport
- Human exposure models
- Dose estimation models

I would suggest that the category "sub-model" or "parameter model" be included as a first model category that provides critical input variables to the above subsequent higher level models. The predominant issue with these types of low level of sub-models would be contaminant sources described as independent variables predicting rates of generation; however, they could also link easily measured or estimated parameters with transport models (*e.g.*, average air speed or air exchange rates and interior dimensional aspect ratios indoors to estimate eddy diffusivity constants). The utility of modeling especially in the nearfield remains quite limited because of the lack of information and parameter development and the subsequent

uncertainty associated with these basic inputs. See review comments above on chapter 5 and research needs.

Exposure estimates being built up from first principle physical-chemical models should be developed and preferred, especially when compared to other types of 'short cut' models such as database/relational or correlation models.

The wording in the Guidelines relative to regression models is awkward as shown below:

> "Statistical models such as regression models based on available data, however, can be used to help estimate the distribution of exposures within a population, including central tendencies and percentiles, or to help quantify the relative significance of factors that can influence exposure levels. These include:"

After the phrase "These include:" four types of "principle-based" (not regression) models are listed. The new reader could miss this distinction.

I agree with Dr. Stern that modeling and monitoring complement and that the notion of treating or considering them as separate camps is "pernicious" to use a term and quote of the late Dr. Joan Dasey (Former Chair of EPA SAB). Clearly, models can show where monitoring is needed and monitoring can be used to ground truth models.

Models, when used as a part of the scientific method can also lead to important discoveries. In attempting to incorporate all of the major predictors of exposure, models sometimes do not come up with good matches to experimental data. These situations represent prime opportunities to learn about the true nature of the physical world that is actually driving exposure. An example of this occurred during the study of isothiazolone off-gassing indoors from treated wood in which, degradation of the active ingredient, previously thought to be minimal, was found to be an important determinant (Jayjock M. A , Deepak R. Doshi, Edwin H. Nungesser, and William D. Shade: Development and Evaluation of a Source/Sink Model of Indoor Air Concentrations from Isothiazolone Treated Wood Used Indoors, Am. Ind. Hyg. Assoc. J. 56 (6): 546-557 (1995).

Rebecca T. Parkin, Ph.D., MPH

Like Chapter 5, this chapter offers broad steps, advice and recommendations for an exposure assessor. Model types are described and key questions for determining their suitability for a specific exposure assessment are discussed. The text seems sufficiently complete and clear for the in-tended audience. The boxes, tables and figures support the text, potentially enhancing readers' comprehension. Most readers can be expected to find this chapter generally helpful as they con-sider which model is suitable for their purposes.

Selection: Section 6.1 is focused on selection of models; additional points are made in Section 6.2. The possible uses and means for evaluating models are described, along with rationales for choosing from the range of simple (screening) models to complex models and more complex, combined models are only noted, not discussed. Means to select among existing models are

presented, but the development of new models is acknowledged as potentially necessary. The authors correctly comment that identifying the type of model depends on the exposure assessment goal, questions and hypotheses, as well as on what estimates are needed and how the model outputs will inform the exposure assessment. The assessor's understanding of the problem statement, conceptual model and exposure path-ways will affect his/her decisions about which modeling approach will be suitable. Working with the assessment team and managers, the assessor also needs to determine the level of output quality which will be sufficient to answer the questions posed. The authors have discussed many major concerns in choosing exposure assessment models.

Use: Refining the model and comparing it to the assessment's DQOs are mentioned early in Section 6.2. The use of models is discussed primarily toward the end of Section 6.2. A variety of models are effectively described along with their best uses; statements about what the disadvantages are in using each type of model are not included. This additional dimension would offer the readers a more balanced context for understanding both the strengths and weaknesses of modeling options. Further, in Section 6.2.2 the implication that complexity is inversely related to utility is simplistic, and likely not correct. "Everything should be as simple as possible, but not simpler," attributed to Einstein, comes to mind as good guidance for choosing a model which addresses the assessment's overarching question/hypothesis sufficiently and efficiently.

Means to evaluate models are covered in Section 6.3, which addresses major topics such as sensitivity and uncertainty analysis, examination of the impacts of assumptions, and attaining QA objectives. Comparing model outcomes with actual measurements is one method to evaluate the validity of a model. The authors advise readers to document the strengths and weaknesses of the models used, in accord with Agency best practices.

P. Barry Ryan, Ph.D.

Following the model of earlier Chapters, Chapter 6. Computational Modeling for Exposure Assessment is a compendium of ideas and guidelines for modeling humane exposure. The first section, Section 6.1 provides some definitions and outlines the approach one should take in modeling of exposure and gives some references that the exposure modeler might find useful.

Section 6.2 gets to the heart of the exposure modeling Chapter. It discusses methodologies for selection of modeling approaches in human exposure assessment and lays out criteria for evaluating the model as a tool. As stated, one must clearly understand one's own objectives before beginning the modeling exercise. For example, is the model to be a screening tool that is generally applicable in many situations, or is it a very detailed model requiring extensive data inputs and validation, but may only be applicable in a limited set of circumstances? The approaches for such diverse systems would be substantially different. Of particular note in Section 6.2 is Table 6-1 that gives a list of exposure resources that are useful to modelers of exposure. This is a valuable resource.

I feel that the Modeling chapter must be tied more closely with the DQO chapter. Modeling must be done to assess whether the DQOs are achievable given what is likely to be found given the uncertainty and variability in the assessed data.

Significant resources can also be found in the discussion of the relationship between modeling complexity and utility for the decision-making process, in particular the graphical representation in Figure 6-1. This paradigm can influence the thinking of the exposure modeler significantly. One may argue with the dichotomy between deterministic models and probabilistic models and their respective utility, however. I am not convinced by the presentation that the authors have made a compelling argument correlating the relationship between complexity, as measured by increasingly probabilistic models, and the utility of such to decision makers. As complexity increases, the models become more difficult to understand and the data ore difficult to obtain and code. I would like to see more discussion in this area. The relationship is not linear and, in fact, may be U-shaped with the optimum utility somewhere in the middle of the complexity curve. I presented this possibility at the face-to-face meeting. It was met with more of a "shrug" than a rousing round of applause, so take it for what it might be worth.

The presentation of differences in certain types of "advanced modeling methods" (which see), is useful. The discussion of one- and two-dimensional Monte Carlo methods is clear enough, as is the discussion of Bayesian approaches. However, the geospatial statistics model discussion is not as well developed and should be. I suggest an expansion of the geospatial discussion beyond the one-to-two sentence description so that it matches more closely the discussions of other methods.

Alan H. Stern, Dr.P.H., DABT

As in other sections, there are issues of complexity relative to audience and intent of use.

Model selection should be driven by the same considerations that drive data-based study design – e.g., specification of the study question. It is too easy to take an off-the-shelf model and run it regardless of whether that model addresses the study question.

The document does a good job in describing the various levels of complexity in models. However, the document does not make a strong point that in terms of model complexity, more complex is not necessarily better, and that model complexity should be fit-to-purpose.

This chapter would benefit from including the graphic from the NAS/NRC publication, "Human Exposure Assessment for Airborne Pollutants (1991)" that lays out the spectrum of exposure models from sources, to external exposure, to internal exposure, to dose, to target organ/tissue.

In the first paragraph of section 6-1, I don't think that the issue is necessarily that models are used because processes are too complex to be captured by empirical data. Rather, models are used when empirical data are incomplete, unavailable, or unobtainable for whatever reason. Also, it is not necessarily the case that there is a dichotomy between data and models, since empirical data are often available and used to inform and ground-truth models. Ideally, models should be used to design data collection/sampling and data collection/sampling should be used

to ground-truth model predictions. This significant overlap should be emphasized more strongly.

In section 6.2.2, descriptions of these modeling approaches should include the potential disadvantages of each approach. For example, for 2-D Monte Carlo, the uncertainty dimension represents the extent of lack of knowledge about the specification of distributions in the first (variability) dimension. However, since the 2-D distributions describe lack of knowledge, they are themselves inherently uncertain and, therefore, not subject to verification or objective quantification. They are, therefore, subject to intentional and unintentional manipulation.

On pg. 125, while it is not clear why detailed descriptions of types of sensitivity analyses for Monte Carlo-type probabilistic analyses are appropriate for the intended level of technical detail in this document, if such descriptions are given, a relatively straightforward and useful approach has been omitted. That is, to set each input, sequentially, to its fixed mean value, rerun the simulation, and note the percent change in a given percentile of the output. The change in the output is a direct reflection of the contribution of each input variable to the variability in the output.

A major omission is the lack of note or discussion of the EPA's computational models for Pb exposure – the IEUBK and All-Ages Lead Models. Not only are these commonly used and useful models, but they are good examples of multilayered computational models. These deserve discussion and links.

Clifford P. Weisel, Ph.D.

The Chapter adequately describes the process for model selection and decisions for using exposure models progressing from screening models to deterministic/mechanistic models to probabilistic based modeling and for data sources that serve as inputs into the models. However, the level of detail given are uneven about the different approaches and there is an underlying assumption that the more complex the model is the better it is. This is not always the case as more complexity requires more detailed input that might not be available leading to more uncertainty. Just a two tier consideration is not always best. The role of uncertainty in the input parameters and how to propagate uncertainty through the models is outlined. The role of QA/QC is highlighted as well. The beginning of the chapter should reiterate that it is important to define the question before being the modeling effort.

The examples (page 113/114) that are provided are for air. Non-air examples should be considered. The statement on page 115, last paragraph, "Some electronic means of recording locations and activities are available" is vague and does not reflect new, evolving technologies. This should be expanded in the measurement chapter on using GPS and smartphone to track people, including the issue of privacy, and then that section should be referenced here.

Review whether references to relevant exposure models and exposure-PBPK models are provided in a clear fashion.

Page 16 last paragraph. Microenvironment can be a location or a behavior, activity pattern that leads to a homogeneous or well characterized environment.

Page 118, 1st paragraph a sentence indicating that biomarkers can be used to evaluate exposure/dose models would be appropriate here.

Page 118 last paragraph 119, 1st paragraph. The discussion with creatinine should include the problems with using creatinine to correct urine. Creatinine formation is really only constant for adults at rest. The validity of urinary correction has been an on-going discussion as to whether the actual concentration of the toxicant in urine, creatinine corrected or specific gravity corrected values are best and it has been suggest that all three be reported and considered in the interpretation of the data and comparison across studies. See for example LaKind, JS, Sobus, JR, Goodman,M, Barr, DB, Fürst,P, Albertini, RJ, Arbuckle,TE, Schoeters,G Tan,YM, Teeguarden,J, Tornero-Velez,R and Weisel, CP, A Proposal for Assessing Study Quality: Biomonitoring, Environmental Epidemiology, and Short-Lived Chemicals (BEES-C) Instrument", Environmental International, 73, 195-207, 2014. PMC4310547. Correction needed for other body fluids should also be included, e.g. lipids in serum and breast milk.

Chapter 7. Planning and Implementing an Observational Human Exposure Measurement Study - provides details on planning an observational human exposure measurement study. These studies are used in parts of the Agency to quantify people's exposures to chemicals in their everyday environments during their routine activities. This chapter discusses the issues surrounding planning an observational human exposure measurement study, including budget and logistical planning, establishing a study design, planning and executing both a pilot study and full field study and the importance of peer review. It also addresses ethical considerations that exposure assessors need to consider when interacting with study participants and the community.

Question 7. Please comment on the discussion of planning and implementing an observational human exposure measurement study.

Paloma Beamer, Ph.D.

This is a very well written and organized Chapter that touches on many important topics that should be considered when you are planning and implementing an exposure study.

It is very good that there is a discussion on determining sample size. However, rather than estimating an effect size that will provide you with statistically significant results it is better to determine what effect size would be meaningful. For example, what difference in fish consumption would be necessary to have a significant difference on health risks? Or what decrease in exposures is necessary for intervention to be successful and warrant the cost? This effect size could then be used to design the study. Furthermore, is there a recommended minimum size, such as n=20 in line with Central Limit Theorem?

While this Chapter does do a nice job on discussing how to engage the community, it should be emphasized that communities need to be treated as partners and key informants. They have knowledge about activities, exposure pathways and sources that would never occur to an exposure assessor not from the community or culture.

Communication with all of the stakeholders outlined on page 132 should be considered and the communication should go both ways. Government organizations like to be informed of university studies being conducted within their jurisdiction, but universities tend to be physically closer to many of the affected communities and may have better local knowledge and community relationships than government agencies in a distant regional office. It is also essential to consider developing a list of stakeholders who should be informed of the study even if they are not engaged in the study.

It is great that there is a section on data analysis and database design. All too often these are considered after the data is all collected. However, guidance should be provided on data entry considerations and appropriate QA/QC measures such as double entry to reduce error.

The IRB considerations and requirements should be laid out more directly. Exposure scientists can come from all different scientific backgrounds and disciplines. Many of these fields, such as environmental science, do not traditionally interact with humans and some of these scientists

may not have experience with IRB or realize that it relates to them. Many exposure studies are considered exempt by IRB, but it is still essential to submit a protocol and have the IRB make that decision.

Nicole Cardello Deziel, Ph.D., MHS

This is a well-written and useful chapter. Box 7-1 has fairly old, classic exposure studies and could be updated. For example, there have been more recent exposure studies and epidemiologic studies with rich, multi-media exposure assessments, such as CHAMACOS or the National Children's Study.

In addition, I think it should be made clear that if the observational study were to be conducted within the context of an epidemiologic investigation, there is a whole other level of design considerations that should be undertaken and refer the readers to Exposure Assessment in Environmental Epidemiology edited by Mark J. Nieuwenhuijsen (2nd edition, 2015).

The section on sample size (7.2.3) is an important piece, and I think it could be strengthened by including a brief discussion on the balance between selection more people/homes/sampling locations with one measurement each, versus having fewer overall participants with multiple samples per person, depending on the time window one wishes to integrate over and budgetary constraints. If exposures are episodic, such as with bisphenol-A, then perhaps multiple measures per person would more important and informative than having more people. If an exposure is somewhat stable or if only short-term exposures are being estimated, then a single measure per person may be adequate.

Penelope A. Fenner-Crisp, Ph.D., DABT

This chapter reflects a balanced and appropriately detailed presentation of the issues. I have no suggestions for modifications except, perhaps, to add more detail on the criteria and their application in the judging of quality of the data gathered in this kind of study.

Christopher W. Greene, M.S.

As an individual who does not design observational human exposure measurement studies, the first question I had when reading this chapter was exactly what media measurements constitute an "observational" study. Although it is not mentioned explicitly in the text, I thought measurements of a chemical in food or personal care products, for example, would constitute observational exposure measurement. Is this true? The chapter did not seem to rule that out, but the focus of the chapter is definitely more on studies aimed at environmental and personal data. I think some text should be added at the start of the chapter to define the spectrum of sampled media covered by this chapter.

I appreciated the use of some examples in this chapter, such as in section 7.2.2. In Box 7-1, the reader would be better served by including a sentence on each of the items, explaining what the study entailed, which is not always clear from the title provided.

Additional comments are provided in the table at the end of this document.

Michael A. Jayjock, Ph.D., CIH

Like the other chapters I found this one to be well written and comprehensive. Comments below deal with possible improvement.

The first sentence of the second paragraph of this chapter states:

> Data generated in an observational human exposure measurement study also can be used to evaluate and refine exposure and dose models

It appears to be true that these data can be used to evaluate dose models and exposure models based on regression analysis but they cannot be used to refine physical-chemical based exposure models unless the same predictors or drivers of exposure in the model are also reasonably characterized and reported as part of the study. This point should be made in the guidelines.

This chapter appears to be understandably biased toward measured as opposed to modeled exposure. I believe that this comes from the current state of uncertainty in modeling compared to the relative confidence provided by monitoring. However, deriving useful estimates of exposure via observation and modeling would presumably be possible given the reasonable development of current models. As such, I believe there may be circumstances where the planning process should include weighing the cost and future usefulness of a large monitoring study versus an observational study paired with a research study to deliver a model that would be useful for the question(s) at hand and have future utility as well. If this possibility seems reasonable to the authors, I would encourage including it in the text.

Rebecca T. Parkin, Ph.D., MPH

While this is an informative chapter, there are several elements which could make it more useful to the reader. For example, the points about obtaining appropriate institutional human subject review board approvals are so important (noted with "must" verbs) that they merit a box or bullets in the text. These necessary steps deserve more obvious flagging in this chapter. No observational human study can begin without these approvals.

Planning: Section 7.2 discusses many of the crucial practical and ethical issues in conducting observational human studies. Ensuring that a sufficient sample size can be obtained for meaningful and interpretable data, within available resources, is a major step in determining whether a study is feasible and necessary. Recruitment of participants in an equitable and fair manner is essential, as is ensuring that the informed consent and assent processes are ethical. Confidentiality, privacy and compensation concerns, all critical elements, are included in this section. The mandatory reviews by all relevant governing institutional review boards help to ensure that both scientific and ethical questions are effectively considered and addressed to ensure compliance during the conduct of both pilot and full studies. Establishing DQOs and proper chain of custody and other methods are practical aspects of human studies. Addressing these issues thoughtfully increases the likelihood of obtaining data that will meet both

performance and acceptability criteria. The discussion of these scientific and ethical topics provides a good orientation for readers unfamiliar with human study elements and requirements. It would also be useful to point out that whenever an exposure assessment will involve health data an environmental epidemiologist should be included on the project team. There are numerous design and data issues which are beyond the training of most environmental and exposure monitoring experts.

Section 7.2.3 does not point out the differences between the number of samples/person (temporal variation) and the number of persons sampled (population variation). This distinction needs to be addressed when sample size issues are being considered in the context of addressing the assessment's overarching question/hypothesis.

Section 7.2.8 contains sound information about engaging the community. Major problems in this and Section 7.2.9, however, are the definitions of "community" and "stakeholder." The title of the latter section implies that communities are stakeholders; this is not the view presented in other parts of this draft (e.g., compare the approaches on pp. 30, 131, 164, 165 and 168). These two terms are used so often in the draft that it is imperative to have consistent definitions for both of them. To achieve clarity and agreement across all chapters, the authors are urged to determine and state clearly whether they consider communities, or a specific subset thereof, within the term "stakeholders" or whether they see "community" and "stakeholder" as mutually exclusive. The differences in definition throughout this draft especially affect how the authors present points about communication strategies and methods for "external" third parties. The members of "stakeholders" with or without "communities" will typically have differ in their perspectives, interests and communication needs. Therefore, communication strategies should be quite different depending on how these two terms are defined. Resolving these definitional issues is essential.

As noted for Section 3.1.3, however, EPA documents have various definitions for these terms. (E.g., the source cited on p. 131 [EPA, 2001h - for which the link is now broken] is more outdated than the citations in Section 3.1.3.) Two definitional options to consider are available at: EPA's International Cooperation, Public Participation Guide website (https://www.epa.gov/international-cooperation/public-participation-guide-glossary-guide-terms on August 4, 2016) and EPA's environmental justice PORT site (DRAFT Environmental Justice Primer for Ports, (https://19january2017snapshot.epa.gov/sites/production/files/2016-07/documents/420p16002.pdf on August 4, 2016).

Sections 7.2.11-7.2.13 provide cogent advice about sampling, data analysis and management. Pilot testing the database before conducting the full study is noted as "imperative" (p. 137), suggesting that this step should be highlighted or included in a Key Points summary of this chapter. Similarly, many statements in this chapter use urgency terms (e.g., must, critical, crucial, essential, imperative, key) pointing to issues which the reader should readily recall after reading this chapter. There are so many concerns, however, that a review may reveal that not all of them are equally urgent. For those points which merit highlighting, an effective device needs to be designed to pull them out of the text explicitly. A table and/or box, in addition to a Key Point summary, may be good inclusions to improve the reader's comprehension of priority issues in human study design and implementation.

Implementation: A substantive issue which can be addressed with minimal editing involves the statement in Section 7.2.10 (p. 133) about the HSRB. The October 2007 meeting of the Board included a discussion of SEAOES; the Board provided positive comments along with many suggestions for improvements. Because "endorse" can imply advocacy of the document, this word is too strong to reflect accurately the HSRB's review of SEAOES. The Board-related sentence in the SEAOES Acknowledgements is correct. It states: "The EPA Human Studies Review Board, a Federal advisory committee, reviewed the external review draft document and provided advice and recommendations that were addressed in the final revision of the document" (SEAOES, p. vi). Note that some, not all, recommendations were implemented, although the Agency likely considered them all in their revision process. The final draft of these *Guidelines* should not include the word "endorse," as it would misrepresent the HSRB's actions related to SEAOES. More precise wording is needed.

Section 7.3.3 mentions pilot testing communication methods and materials. That is an important step, which merits emphasis here. Additionally, the text should refer back to wherever communication strategy development is described and where pilot testing plans need to be explicitly included. Without pilot testing, major errors may be made, damaging trust between the assessors, stakeholders and/or communities. For example, note that "to whom," rather than "with whom," is used in the text (p. 138, 7.3.3 first paragraph, line 10). This implies a unidirectional approach which is not now considered "communication" and is likely to be unsuccessful. This phrasing may have been an unintentional error by the author of this section but it needs correction to align with current concepts of communication. The erroneous use of "to" was found in other chapters, where it needs to be addressed as well.

The description of "peer review" in Section 7.5 is largely consistent with Section 5.2, but it offers additional focus on ensuring that work products "meet the highest quality and ethical standards." This addition is a very important part of the peer review process; it deserves more discussion in the *Guidelines*.

P. Barry Ryan, Ph.D.

Chapter 7. Planning and Implementing an Observational Human Exposure Measurement Study presents a series of common-sense guidelines in the planning and development of exposure studies. It is somewhat redundant with other Chapters, most notably Chapter 3. Planning and Scoping and Problem Formulation. Comments I have given there apply to this Chapter as well.

I think one of the most important sections of this Chapter is Section 7.2.1 Budget and Logistical Planning, yet it is one of the shortest. The focus of this section- the utility of underfunded studies- needs expansion. Studies that are substantially underfunded do not increase the efficiency of the study. In order to fulfill certain objectives a certain amount of money must be spent. Restricting the resources results in a study that may not fulfill the DQOs needed by the Risk Manager and result in a significant waste of scarce resources. Appropriately funded studies produce valid results that can be used by regulators and that are defensible to the scientific community. I think expansion of this section is warranted. Note that on Page 129 Paragraph 4, the authors support this contention by stating "… The number of participants enrolled in a study often is a compromise between the budget available for the study and the power the study can

achieve…." As I often tell my students, the sample size calculation most relevant is field studies is the total budget divided by the cost per sample. Statistical significance and power is then calculated based on this reality. Clearly, this is opposite the appropriate strategy. A discussion of such would be of interest; one sentence is not enough. I do not mean this to be a facetious discussion, but rather an exaggeration for effect. Budgetary restrictions are always with us and must be taken into account.

I have little to add beyond this statement, as the authors have described in some detail the steps beyond the statistical analysis component that must be considered in developing a study. I note that they emphasize the need to include stakeholders in the design phase and that human subjects and ethical considerations are paramount. This is a strong statement that is well emphasized in this document.

Section 7.3 Planning and Executing a Pilot Study is of importance, but often ignored. USEPA-funded studies are better at supporting this than other Federal and private agencies. The importance of beginning a study with a pilot-level investigation needs support in the literature. Rushing into a large investigation is fraught with danger. I commend the authors for including this suggestion. One problem however, is using the TEAM investigation as the example. The TEAM investigation, albeit and excellent study, is now 30 years old. A more modern reference may add to the relevance.

Section 7.3.2 should include specific reference to lessons learned from the pilot investigation. It speaks to the documents, but not the study itself. Protocols should be modified and implemented. Also, the protocols should be flexible enough to afford change after the large-scale investigation begins. Compare with Phase II and Phase III clinical trials. This is an important outcome of the pilot-level investigation.

Alan H. Stern, Dr.P.H., DABT

In Section 7.2.3, it is surprising that power calculations are not mentioned.

The description of "effect size" is a large oversimplification, and as such, may not be practically useful.

On pg. 135, second paragraph, in the discussion of compensation and incentives for participants, the text should add study-related services such as medical exams.

The information on QA/QC, field, trip and lab blanks in Section 7.2.12 is largely a repeat of information presented in Chapter 5.

Clifford P. Weisel, Ph.D.

The chapter is organized in a rationale fashion, highlighting the key components of planning and conducting observational human exposure studies. These include identifying critical elements, determining the sample size, recruitment, community engagement, identifying the tools/protocols, pilot study, implementation and communication. Availability of resources is

addressed, since that can be significant for large studies; and human subjects considerations are discussed which can have major impact on the study. A warning should be included explicitly stating that the protocols being used are for an observational study and the participants are not exposed to any agents because of their being part of the study.

The reader should be informed that investigators being present to observe the subjects might influence the participants' behavior and advice given on steps to minimize or avoid that happening. Anecdotal stories exist of how participants will clean their home more than typical before the researchers come to sample as they consider them guests they have to prepare for; children who are videotaped change their behavior because they are in front of a camera; the food selected for a meal is healthier than typical when a subject knows dietary samples are being collected, etc.

Page 127, paragraph 1 states that ADME are not studied in human exposure measurement studies, but the next paragraph suggests that the study can be used to refine exposure and dose models. To refine dose models information on ADME is needed. When biomarkers are included in the exposure study ADME should be determined.

A reminder to engage the community and stakeholders to be part of the planning and design process is warranted.

Chapter 8. Uncertainty and Variability in Exposure Assessment - considers uncertainty and variability in exposure assessments, incorporating them into planning, scoping and problem formulation (Chapter 3) and data quality objectives (Chapter 5). This chapter highlights how these concepts are used in the application of models in an exposure assessment.

Question 8. Does chapter 8 provide sufficient guidance on considering and communicating uncertainty and variability in exposure assessment? If not, what additional content should the chapter include?

Paloma Beamer, Ph.D.

Chapter 8 is an essential chapter on a topic that is difficult for many to understand and grasp. As emphasized in the Chapter it is also important to have transparency in the communication of these methods. However, this Chapter is currently difficult to read because of the flow and the use of jargon that may be unfamiliar to someone who is not already an expert in probabilistic exposure models.

Although there is a very nice list of definitions early on, many terms such as 2D MCA are used without definition until much later in the Chapter. It would be important to go through the Chapter and identify all of the terms that are used and include them in the list at the beginning.

A little more information is needed to differentiate 1D and 2D Monte-Carlo analysis for the novice modeler. It would also be good to explain in more layman's terms what the benefits and limitations of each one are and what kind of data is needed to conduct them.

This chapter needs a better justification of not only what is meant by variability, uncertainty and sensitivity analyses but also why it is important for exposure assessors to consider them. Essentially, while the details of these topics are beyond the scope of the Chapter, rationale should be provided that will motivate exposure assessors not familiar with topic to learn about these topics and read the more detailed resources.

This chapter should consider providing some simple examples (including figures) that demonstrate the utility of these sorts of analyses. For example, there is an excellent one for sensitivity analyses on EPA's website (https://archive.epa.gov/epa/measurements-modeling/sensitivity-and-uncertainty-analyses-training-module.html). Another good and even simpler example is on pg. 3-30 of the EPA document "Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment" (https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=157668&CFID=76584772&CFTOKEN =95143963).

Some guidance on how to fit probability distributions to data should be provided, as well as many of the good EPA references on this topic. For example, the document titled "Options for Development of Parametric Probability Distributions for Exposure Factors" (https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20867). This may also fit well in Chapter 6.

Nicole Cardello Deziel, Ph.D., MHS

This is an important chapter, as the credibility and interpretation of an exposure assessment depends upon robust and transparent methods and assumptions. I agree with comments by Dr. Weisel and other panel members that a greater distinction between the concepts of uncertainty and variability would strengthen this chapter.

The presentation of sensitivity analyses could be improved. The definition for "sensitivity analysis" in Box 8-1 (p 142), which is from a 15-year old document, was non-intuitive and is quite vague ("common sense" technique). In addition, details about sensitivity analyses appear in different places. Sensitivity analyses could serve different purposes—to test how robust results are to variations in assumptions and inputs as well as identify key sources of variability or uncertainty, inform model refinement. I think a clearer discussion of this would be useful.

It would be useful for EPA to explicitly discuss its approach to conservativism/plausible conservatism; i.e., that in the face of uncertainty, assumptions and default values should be scientifically supported and public-health protective. To be public health protective, exposure assessors should not err on the side of underestimating exposures for risk assessments.

Penelope A. Fenner-Crisp, Ph.D., DABT

I found the three introductory paragraphs to this chapter to be rather cumbersome and confusing. I would suggest striking those paragraphs and depending, instead, upon the discussion in the topic-specific sections that follow. Most of what is covered in the introduction is presented in these sections in a much clearer and transparent way.

I don't expect this Chapter to tell/show me, in detail, how to conduct an uncertainty or variability analysis. However, I do expect there to be enough background information in it to get a good sense of what and how the Agency is thinking about this issue. For the most part, I am comfortable with the level of detail, although I would like to be assured that the Chapter cites all of the relevant Agency documentation and key references authored by others. It also would be helpful to include a few examples of actual analyses that the Agency has performed in the recent past. Just a few lines about each and the link to the relevant document.

In addition, there should be a discussion of the decision criteria used to determine if/when an uncertainty analysis will be conducted. This discussion might best fit in Section 8.2.1.

Page 141, paragraph 3: I would suggest revising the first sentence to read "EPA ~~consistently~~ has acknowledged ~~addressed~~ the need to characterize uncertainty in risk estimates." "Addressing the need" has not necessarily translated into actually conducting uncertainty analyses in specific cases as often as the NAS/NRC and others have recommended.

Christopher W. Greene, M.S.

Overall, I thought this was a good overview of the issues around uncertainty and variability, a difficult topic that most of us encounter in our work. The main issue I had with the text was with

the definitions in the first couple of pages, and how uncertainty, decision uncertainty, data uncertainty, and variability relate to one another. The definitions in Box 8-1 attempt to define key terms, but the text preceding the table had me going in circles as to what subclasses of uncertainty fell under what broader types of uncertainty.

Table 8-1 (not Box 8-1) was very good because it concisely defined the contributing errors and provided some examples.

Figure 8-1 (not Box 8-1 or Table 8-1) could use a redesign or more explanatory text. As proposed for exposure assessment documents sin Chapter 9, figures should be self-explanatory whenever possible. I wasn't sure how this figure communicated uncertainty resulting from limitations in data analysis. With some redesign, it could be an illustration of measurement uncertainty (which I think was the intent of the writers.)

The coverage of the topic was quite thorough, but I also thought that parameter sensitivity (in the modeling sense) was a topic worth some attention in this section.

Other comments are provided in the table below, under "Specific Observations."

Michael A. Jayjock, Ph.D., CIH

I found that this chapter provides a credible discussion of the topic. I particularly appreciate the discussion of the importance of sensitivity analysis.

One area that I believe could use some additional explanation is in the almost unavoidable comingling of uncertainty and variability inherent in the process when, as assessors, we attempt to use a range or probability distribution to describe any critical exposure driver. It is important to remember, and to state as part of the guidelines, that any assigned range or distribution represents our best portrayal of reality based on available data and expert judgement. Indeed, depending on the quantity and quality of the data, the range or distribution could be almost purely inherent variability on the high end or dramatically driven by our lack of knowledge on the low end of quality. The example I often use with my students is the **estimation of the weight of my dog**, **Libby**. I present the example below just to explain the point. I leave it to the authors of the guidelines as to how they might want to express this important and ubiquitous situation in exposure/risk assessment which I believe should be explained in detail within the document.

Stages and assigned distributions for Libby's weight:

Assumption: we want to error on the side of **overestimation**.

Stage 1: no information other than Libby is a dog. Typical **range** or **uniform** probability distribution function (PDF) 5-150 lbs

Stage 2: **more info** Libby is a full grown Springer Spaniel. PDF **normal** distribution mean 50 lbs, SD = 10.

Stage 3: **we measure Libby** every day for a month. PDF **normal** distribution mean 40 lbs, SD = 1.05.

Stage 1 is mostly uncertainty bounded by expert judgement. Stage 3 is almost all variability. In my experience, Stages 1 and 2 are typical of most parameters in an exposure assessment, these estimates are not reality, but they represent our best portrayal as assessors of the reality of, in this example, Libby's weight.

Stage 1 may be acceptable given the question at hand and, in the context of exposure assessment, the toxicological benchmark(s) show(s) potency less than worst case estimated exposure.

As is mentioned in the guidelines, Baysian techniques can be used to incorporate expert judgement into the assignment of PDFs.

One advantage of uncertainty analysis that could be explored more in the guidelines is the message it sends to those using the results for decision making. The process clearly shows the relative lack of confidence in a single value prediction of risk and the value of information to increase that confidence.

The explicit point should be made that sensitivity analysis reveals the most important drivers of exposure. Further expert opinion analyses of these drivers identify and separate uncertainty from variability within those variables. This activity will help direct cost effective research that could narrow the distribution of predicted exposure.

Rebecca T. Parkin, Ph.D., MPH

This chapter describes different types and sources of uncertainty in exposure assessment. Variability is discussed to a lesser degree, but its significance is not ignored. The topic with the least coverage is communication. One problem with the chapter is the commingling of uncertainty and variability, which may confuse readers and obscure the distinct points the authors are trying to make. Also, jargon and technical terms (e.g., Latin hypercube) are not suitable for the intended audience.

Guidance on considering uncertainty and variability in exposure assessment: The chapter provides readers with a general orientation to the roles of uncertainty and variability and the methods for evaluating their impacts on exposure estimates. This chapter is not meant to be a step-by-step manual for evaluating the impacts of these two concepts on exposure estimates; it meets that objective sufficiently. Some concerns, however, need to be addressed.

Two questions regarding uncertainty and variability in exposure assessment are asked in the third paragraph of the chapter introduction (lines 2-4); they focus on assumptions and the acceptable level of uncertainty for decision-making. But the underlying question/hypothesis addressed by the exposure assessment is not noted; this is a glaring omission. If the study question was not clearly framed at the outset, its deficiencies will be quite apparent at this stage. Pointing out that lessons need to be stated and next steps determined would be useful guidance.

Several types of uncertainty are described. Although decision uncertainty and data uncertainty are discussed in the second paragraph of the introduction (p. 140), this section needs revision to distinguish these concepts more clearly. Lines 1-3 and 9-10 can be read as conflicting concepts. Furthermore, there are somewhat different definitions of decision uncertainty and data uncertainty throughout Section 8.1. For example, in Box 8-1 data uncertainty "may" be a part of decision uncertainty, but on p. 140 data certainty "is" part of decision uncertainty. Ultimately, the impression is that the authors view data uncertainty as part of decision uncertainty. If the box statement is correct in a universal sense and the "is" statement represents the authors' views for the purposes of this chapter, then those two scales should be made clear to the reader. Without consistent definitions of these terms, the reader is left to guess how the authors define these terms for the exposure assessment process.

The types and sources of uncertainty presented in Table 8-1 complement the text; this table is a useful tool for readers. The cited source supporting this table should be corrected (III below). Figure 8-1, however, is not clear; it should be deleted or revised to support the author's point.

Variability is defined and described in 8.1.3. The impact of variability on the precision of exposure estimates is stated generally in the first paragraph; it would be more informative if this statement were supported by a specific instance in which variability made a difference in the estimate. Human, spatial and temporal variability are briefly described and supported with examples. There are no examples of how these factors would affect estimates, except by implication of the sentence noted in the opening paragraph of 8.1.3.

Methods to evaluate the impacts of uncertainty and variability are presented in Sections 8.2 and 8.3. Questions are posed for consideration and approaches for gathering data to answer those questions are presented. Issues to consider when identifying input parameters, the appropriate level of analysis (screening to probabilistic) and the methods to conduct a sensitivity analysis are described. The fundamental concerns and techniques for assessing the impact of uncertainty and variability are included in this chapter.

The guidance is general but fitting; it offers the reader an overview of the importance of uncertainty and variability in exposure assessment and helps him/her to understand and recognize the levels and purposes of various methods to assess impacts on exposure estimates. The document does not indicate, however, at what point(s) in exposure assessment uncertainty analysis should be done or how to determine whether it should be done.

Guidance on communicating uncertainty and variability in exposure assessment: Section 8.4 is not as well developed as Sections 8.2 and 8.3; it is not sufficient to orient readers only to the range of relevant issues and methods. Communication about uncertainty and variability can be complex; these aspects of the assessment must be presented in ways that stakeholders, managers and communities can understand and to the extent they need and want the information. This important point is not made. Section 8.4 poses some of the questions that assessors should ask of themselves when preparing to share relevant results with the public, but it does not cross-reference the importance of developing a communication strategy early in the exposure assessment process. This crucial first step should be reiterated here; tools are not a replacement for a strategy. Section 3.1.3 begins the *Guideline*'s consideration of communication strategies,

although the discussion there is incomplete (see comments under question 3). The importance of finding out who wants to know about this portion of the exposure assessment, to what level of detail and in what format cannot be under-emphasized. Perhaps the January 2016 Superfund booklet cited earlier will offer the authors more insights for strengthening this section.

In various parts of this chapter, the text mentions both internal (assessor with managers) and external (assessors with stakeholders and community) forms of communication. Section 8.4 addresses both but does not clearly separate them; distinct subsections for internal and external communications would be better. Ensure that the same concepts are covered for each form (e.g., the list of questions on p. 157 is focused on communicating with external parties; there is no comparable list presented for internal communications). Although the final paragraph on p. 157 is reasonable, the instruction to focus on "clearly communicating" is too general to be useful; add depth and resources here.

P. Barry Ryan, Ph.D.

Chapter 8. Uncertainty and Variability in Exposure Assessment focuses on numerous issues associated with determination of uncertainty and variability in exposure assessments. It introduces the term "decision uncertainty" that integrates all levels of both uncertainty and variability throughout the exposure/risk process into the uncertainty in a final policy decision made by decision makers. While this is a new concept for me, it is a clear extrapolation of information and a clear continuation of the process. A clearer definition of the decision uncertainty is warranted beyond that given in the first couple of sentences in the Chapter that gives a definition that I find vague. The definition that rises out of the content of the remainder of the Chapter is clear and should be developed in those first few sentences.

The discussion is relatively complete in the Chapter and I see little need for modification of its structure. There are some details I would like to see filled in, however, above and beyond the decision uncertainty, there is little I find imperative.

Alan H. Stern, Dr.P.H., DABT

While it is necessary to mention uncertainty, variability and probabilistic/Monte Carlo analysis in several contexts in the document, it should only be necessary to discuss it in any detail once, with other sections referring to the primary section.

Many of my comments about the use of 2-D Mont Carlo analysis are included in my comments to Chapter 5. In addition, however, the document should point out that, while 1-D Monte Carlo analysis necessarily includes descriptions of both variability and uncertainty (even if the intent is to address only input variability, the need for 2-D Monte Carlo analysis can be minimized by closely linking the input distributions in a 1-D analysis to the available data. If the available data are not sufficient to support a probabilistic analysis without unwarranted assumptions, the document should state that (as per my comments to Chapter 6), the complexity of the model should be linked to the available information and the purpose of the assessment. Therefore, if uncertainty is too large to support a 1-D analysis, it should be considered that simpler, deterministic approaches can be used.

In addition, it should also be pointed out that uncertainty can be addressed semi-quantitatively (e.g., high, medium, low) for each distribution. Using this approach, the contribution of each input distribution to overall variability in the output can be associated with a descriptor of uncertainty such that an input distribution can have (e.g.) a large contribution to variability and a low amount of uncertainty. Nonetheless, it is not at all clear that the document should even be addressing methods of quantitatively addressing uncertainty in probabilistic analysis other than to say that some assessors do this and supplying a citation.

On pg. 142, the example provided for "exposure scenario uncertainty" is a reasonable example, but it misses the key point that the uncertainty in this example occurs not specifically because the exposure assessment from one part of the country is being applied to another part of the country, but rather, because the extent to which the data from one part of the country is applicable to the other location is *unknown*.

In Table 8-1 (pg. 143), "surrogate data" is a subset of "nonrepresentativeness," not a separate category of data uncertainty.

In Table 8-2 (pg. 146), critical and primary questions regarding decision uncertainty are missing: Was the decision question clearly stated? Was the intent and application of the answer to the decision answer unambiguous? In addition, the sixth question in this table is poorly written and I cannot follow it.

In the fourth bullet on pg. 153, the implication (although not directly articulated) is that screening level *exposure* values are used in a screening *risk assessment* to generate upper bound estimate of risk (cancer risk or HQs). This should be clearly stated.

Clifford P. Weisel, Ph.D.

Overall the chapter is comprehensive and describes how to assess these factors and propagate them. These are particularly important to define when using exposure characterization in risk assessments. The one problem I have with the chapter is the way that the two factors, uncertainty and variability, are interwoven and discussed as equivalent concerns. While the two are properly defined in the beginning of the chapter with the distinction stated "data uncertainty refers to lack of, incomplete or incorrect information, whereas variability refers to true differences in attributes resulting from heterogeneity or diversity in an individual or population." This distinction is less clear as the chapter progresses. What the exposure characterization should do is reduce the uncertainty by improving the measurements or modeling while identifying the variability. The risk analyzer can then decide whether the additional resources needed to reduce uncertainty are warranted. He or she than needs to quantify and understand the variability so an appropriate risk can be assigned. I suggest that these two factors be in separate sections in the chapter rather than combined. The section on how to deal with and use each should be discussed separately, relative to the implication that each has in a risk assessment. The different meanings of these two factors should also be clarified when communicating results to the public, as is discussed in Chapter 9.

Section 8.3.3 on Sensitivity Analysis needs to be reviewed as it suggest that it is a common sense technique that involves probabilistic risk assessment and advanced modeling tools.

Chapter 9. Presenting and Communicating Results - highlights communication, emphasizing the importance of identifying the intended audience, the types of communication products, communication strategies that might be appropriate for different exposure assessments and related ethical considerations.

Question 9. Please comment on the discussion of communicating exposure and risks.

Paloma Beamer, Ph.D.

Chapter 9 is a well-organized and well-written chapter. It is good that the importance of communication of results is emphasized at the beginning. It does not matter how well the exposure assessment was done if the results cannot be communicated effectively to the affected community.

Communication strategies need to be developed at the beginning of an exposure assessment, not just in the results report back phase. It is essential to decide at the onset and be very clear if the assessment is going to be able to give information related to health risks or not. The communication strategy also needs to relate back to the community's needs assessment and their risk perceptions. Fundamentally, it is all about building and maintaining trust with the community and the stakeholders. If there is no trust, then it is not likely that the results will be communicated and understood effectively.

Guidance should be provided on assessing the basic "reasonableness" of the results and for review by an expert not involved in the study to ensure that there are no obvious errors before results are released. For example, did the calculations results in soil screening values that exceed 1,000,000 ppm? Developing some guidance on simple rules-of-thumb that can be used as checklist will be beneficial to many current risk assessments.

Guidance should also be provided on how to get input on the results communication process and materials form the affected community and/or the targeted audience. For example, materials could be piloted with community informants or an advisory board. They can often times provide very helpful input on language and figures.

Table 9-1 provides a nice start for providing guidance on good risk communication. It would benefit from having more balance between concrete "good" and "bad" examples.

The section of Table 9-1 on credible versus non-credible sources also needs to be more specific. Not all industry data is non-credible (sometimes it is the only data) and not all government or academic data is necessarily credible. Better guidance should be provided on what makes data credible, such as "peer review" or use of "standardized procedures."

While there are references in the Chapter to other documents that provide examples of good communication materials, it would be useful to have a few examples of good graphs or infographics within this Chapter from those references to help highlight their usefulness.

Because many times it can take months to years to complete an exposure assessment, guidance should also be provided on how to develop a communication plan/protocol while the exposure study is ongoing. For examples, are there levels of blood lead or urinary arsenic in a child that should be of immediate concern and warrant communication with the parent prior to the entire study being completed?

A key step in communicating exposures and risks should also be the assessment of any advice that you can tell the public or affected community about they themselves can do to mitigate or reduce exposures. In particular, this helps communities feel empowered rather than disempowered and apathetic when there are documented exposures of concern in their community.

Nicole Cardello Deziel, Ph.D., MHS

I found section 9.3 on the media to be unnecessarily harsh and perhaps these bullets could be revised to be more constructive with some "How Tos" of talking to the media. For example, having three key messages.

This chapter, such as Section 9.6, could include some updated references. Many researchers are actively engaged in communicating exposure results to the community. Below are some other references I have found helpful for communicating exposure assessment results to community members.

The chapter highlights the importance of using graphics to communicate findings. It would be beneficial if these guidelines included examples of Fact Sheets or Exposure Reports or other communication graphics, reports, etc. The Haynes et al. paper in EHP below included some of their materials in the Supplemental Material. If EPA has some similar materials, that would be useful.

Based on the in-person panel discussions, it may be useful for EPA to offer suggestions for communicating exposure assessment results when the risks are not yet known as well as when they are part of an overall risk assessment. I think both are plausible scenarios, particularly for non-EPA researchers.

Brody, J.G.; Dunagan S.C., Morello-Frosch, R.;Brown, P.; Patton, S.; Rudel, R.A. Reporting individual results for biomonitoring and environmental exposures: lessons learned from environmental communication case studies. Environmental Health 2014, 13(40).

Haynes, EN, Elam, S, Burns R, Spencer A, Yancey E, Kuhnell P, Alden J, Walton M, Reynolds V, Newman N, Wright RO, Parsons PJ, Praamsma ML, Palmer CD, Dietrich KN. Community engagement and data disclosure in environmental health research. Environ Health Perspect. 2016 Feb;124(2):A24-7. doi: 10.1289/ehp.1510411.

Penelope A. Fenner-Crisp, Ph.D., DABT

This chapter does a good job of covering the important aspects of communication. Importantly, it provides additional resources to support further inquiry.

Christopher W. Greene, M.S.

Overall, I thought this chapter was well done. I identified a few areas that could stand to be expanded, and a few communication-related topics that should be addressed.

In the second paragraph on page 160 the report states that "stakeholders might hold a more complicated view of risk than do technical experts." I thought this was an important observation and worthy of expansion in the text.

Many governments, government agencies, and other institutions have policies relating to accessibility of public documents to the disabled, particularly visually impaired persons who use screen readers to reflow documents and read them aloud. I think this document should include general advice on this topic, with links to more in-depth information. At the Peer Review Panel meeting, the writers did confirm that the final Guidelines document will itself be in an accessible format.

Another issue that is often encountered with public documents is the management of documents that may become part of a public record and remain available for many years, while the state of the science advances. These issues can be managed through the addition of expiration dates to existing guidance, along with an internal process of periodic review. Some discussion of this issue (management of legacy documents) could be useful.

Communication of exposure assessment results with the public must also strive for consistency with messages being sent out by other units or workgroups in the same agency or institution. This is a potential hazard for exposure assessments of chemicals that cross disciplines; for example, statements about pesticide exposure may come from exposure and risk assessors, agriculture departments, and/or health departments.

Additional comments are provided below, under "Specific Observations."

Michael A. Jayjock, Ph.D., CIH

The information in this chapter is way beyond my normal area expertise; however, it is an area of interest and I have had occasion to communicate exposure and risks mostly to clients. As is well stated in the chapter, I always present results in the context of uncertainty. Again, all of the points made within this chapter seem to me to be quite valid and born of a lot of experience and developed expertise within the Agency.

It is worth mentioning in the Guidelines document that communicating uncertainty in an exposure/risk assessment, when it is very high, can be somewhat embarrassing to disclose, but should be stated explicitly as an integral part of the integrity of the process. For example, the

statement could be that the putative risk from this estimated exposure could range from zero to the reasonable worst case values that are being reporting here. On the other hand it is important to note that risk assessments do not typically get written with a conclusion of unacceptable risk for the situation as is or with the invocation of risk management. Work has to be done to get the exposure/risk assessment to this point.

I always make the point during communication of results that, as a professional and ethical issue, I have traded conservatism for data such that the putative exposure and risk is purposely biased to be higher than the true risk. I also inform them that the difference between the estimated or assigned risk and true risk is inversely related to the amount of confident knowledge we have in the predictors of exposure.

Rebecca T. Parkin, Ph.D., MPH

The title of this chapter is narrowed to the communication of exposure assessment results; the chapter is not intended to cover the broad range of communication challenges that may occur throughout an assessment. Chapter 3 is a good place for discussing earlier communications both within the study team, with managers and with external parties; some of that discussion occurs there. Section 9.1, however, begins focusing on the communication of results and then goes more broadly to communication strategy (which should be updated and expanded in Section 3.4) and then risk communication, of which exposure assessment communication is a part. Either the chapter title or content needs to be revised to make them congruent. If only communication of results is the intended scope, then 1) the discussion of strategy should be limited to Section 3.4 and 2) risk communication should be presented as the umbrella for results communication and limited to the introduction of this chapter. The last paragraph in Section 9.1 could be expanded and placed as the first paragraph of this chapter's introduction. There is no mention of whether communication strategies are different depending on the exposure assessment context (e.g., stand-alone activity or part of a comprehensive risk assessment).

Strikingly, there is no definition of "communication" anywhere in this document; this may be part of the reason why the concept is presented and discussed somewhat differently across the chapters. Sometimes the term is used for internal communications, sometimes for external ones, sometimes for one-way methods and sometimes for more complex interactions (possibly meant by the terms "engaging" and "involving" external parties). A clear definition and citation for "communication" should be in the introduction to this chapter and in Section 3.4 and used by all chapter authors. This is another example of a term which belongs in a glossary.

At several points in this chapter (as in Section 7.3.3), the word "to" is used when describing the exchange of results between assessors and other parties; this term is only appropriate when one-way methods are envisioned. Whenever interactions should also include receiving questions and comments back from other parties the word "with" is more contemporary and advisable. This may seem like a small point, but this one word can make a big difference, affecting how other parties perceive assessors' communication efforts and whether they feel respected as legitimate and engaged parties in the process.

The title of Section 9.4 is not correct; strategies do not follow products, products are elements which derive from the strategy. The section actually focuses on tactics (how-to's), rather than strategies. The last paragraph of Section 9.4 discusses tools (or tactics) to implement the strategy. This paragraph should more clearly state that tools are developed after a strategy has been designed; tools alone do not constitute a strategy. Table 9-1 presents tactical "lessons learned," which are not entirely supported by peer-reviewed risk perception and communication research. Deleting this table and replacing it with content based on the January 2016 Superfund handbook (cited earlier) would be more useful and contemporary.

Section 9.4 may reflect current practices, but it needs to refer to the Superfund handbook as a more recent resource concerning the definition, components and methods for developing a well-conceived and structured communication strategy. The many parties, issues and interests involved in exposure assessment point to the need for a communication strategy early in the entire process.

The ethics questions raised and advice offered are limited in Section 9.5. Changing "need to be approved" to "must be approved" in line 3 would more clearly emphasize the mandatory nature of IRB approvals. In addition to drawing on the January 2016 Superfund document, this paragraph could be strengthened by utilizing material in the SEAOES document (Sections 6 and 7), namely definitions of "communication" and "community," discussion of ethics questions in human studies, and descriptions of the elements for a substantive communication strategy. Further, the last sentence of Section 9.5 needs to be revised, making it more specific. The current version of this sentence does not point the reader to resources to help him/her understand the ethical issues in communicating risks.

Section 9.6 lists resources but does not indicate which of these may contain useful discussions of ethics or (as stated at the end of 9.4) which sources focus on communication strategies. A table or more refined presentation of the resources in 9.6 is needed. The "array of published literature," which is in the thousands of items at this point, is daunting. The reader will need more specific guidance to locate the most suitable and scientifically reliable literature for meeting the assessment's objectives.

Communicating exposures: The elements of exposure characterization, methods to convey them and the special issue of expressing uncertainty in meaningful ways are covered in Sections 9.2-9.4. The content of these sections is generally sound and supported by citations, but some of the links are not functional now.

Section 9.3 considers parties with whom assessors communicate in separate subsections; this is a good approach because each of these groups likely has different needs and interests. Assessors must be aware of and thoughtfully tend to these concerns. The opening to Section 9.3 splits stakeholders and communities as separate "audiences," implying that one-way communications are intended; however, rarely will these two groups want one-way means of communication. An updated term needs to replace the passive "audiences." Subsequently, in the first paragraph of Section 9.3.2, stakeholders and communities are blended together; "communities" are viewed as one part of "stakeholders." Here is an example within one chapter of these two groups being

handled differently; this inconsistency needs to be resolved. The end of this same paragraph offers a good statement of an effective communication approach with "the community."

Communicating risks: The last full paragraph in 9.2.1 speaks to communication throughout the risk assessment process. This seems misplaced; it may be better at the beginning of this section. A broad discussion of risk characterization which narrows down to the role of exposure characterization in risk characterization would provide a more logical segue into Section 9.2.2. A thoughtful reorganization of Section 9.2.1 is advisable.

The focus of this chapter is not really about communicating risks at the end of the risk assessment process. The entire chapter should be clearly focused on communicating exposure assessment as part of the risk assessment process.

P. Barry Ryan, Ph.D.

This is not my area of expertise at all. I can only make the most general of comments.

This Chapter appears redundant with sections of several other Chapters. Can it be removed, or the sections addressing communications be removed from the other Chapters? It seems quite redundant.

Does Box 9-1 belong here? It is a statement of EPA Policy that might have best been seen elsewhere.

Alan H. Stern, Dr.P.H., DABT

It does not seem likely to me that the results of an exposure assessment would be communicated to the public in isolation. If they were there would be no context with which to determine the significance and relevance of the results. It is more likely that an exposure assessment would be reported as part of an overall risk assessment. This chapter should be structured with that in mind.

Clifford P. Weisel, Ph.D.

The need to engage communities and have a valid plan for communication is an important component of an exposure assessment, particularly one that will be used in risk assessment and management. Thus, it is appropriate for the guidance document to not only have sections in most chapters on this issue but also full chapter that can be referenced. The chapter is reasonably organized and utilizes existing concepts and reference resources that are common for developing a communication plan. Good communication is an underlying principle of a successful exposure assessment so the generic principles that have been developed for these activities apply for exposure assessment.

Communication about an exposure assessment is rarely done without a discussion of risk or health related to the agent being considered. The chapter should address those links and

approaches to deal with issues of health when the focus of the communication is about the exposures.

What is the definition of communication that is being used here and in other parts of the guidelines?

The language of the chapter should be reviewed to better relate that communication should be with the community and stakeholders as an interactive enterprise and not to the community from the scientist or risk assessor.

Consideration of whether this chapter should be about communication throughout the entire exposure assessment process, from the developing of the project to relating finding results or on communication exposure and risk.

The one additional section that might be considered is how to establish an on-going communication if a risk management plan is put in place to reduce exposures and subsequent exposure characterization is done to evaluate how effective that plan was.

Additional Comments

Question 10. The peer reviewers can provide any additional comments that they feel would benefit the draft document.

Paloma Beamer, Ph.D.

In progress

Nicole Cardello Deziel, Ph.D., MHS

See specific comments.

Penelope A. Fenner-Crisp, Ph.D., DABT

This Panel and other commenters have recommended both small and significant modifications be made to these draft Guidelines. In light of the many changes proposed and options cited above for the scope of the next iteration of this document, I believe that the revision(s) to this draft document also should be subjected to external peer review and public comment, before being completed. There is precedence for bringing the next version of a product back to the same peer review panel; both the SAB and the SAP have been reconvened on a number of occasions over the years.

I was disappointed to see that there were no workgroup members from OCSPP. Is OCSPP experience/point of view adequately captured in this document? I don't think so. This may become a glaring omission, given the enormous amount of science policy and guidance developed or forthcoming in response to the mandates of FQPA and the recent passage of amendments to TSCA, both of which have resulted, or will result, in a much greater level of risk assessment activity in OPP and OPPT, respectively.

A recommendation for a Follow-up initiative: Develop and execute an educational program targeted to parties who currently do NOT perform their research or other information-gathering activities in accordance with EPA policies and procedures.

These Guidelines describe the principles, policies and practices that steer the Agency's exposure assessment activities. As noted in the Executive Summary, in addition to applying to the Agency itself, they also would apply to those "who perform this type of work under Agency contract or sponsorship, as well as academic, industrial and others who perform this type of work in accordance with EPA policies and procedures." While the Agency does design and conduct or sponsor exposure (and toxicity) studies with the expectation that they will play a significant role in its research, risk assessment and decision-making activities, in reality, EPA often must depend upon data generated by outside parties (e.g., academic, industry and others) who do NOT perform this type of work in accordance with EPA policies and procedures.

There currently is a rigorous debate underway in the scientific community concerning the role that non-conforming research results and other information should play in the Agency's risk

assessment and decision-making processes. This debate is perpetuated primarily by academics who argue that their peer-reviewed (i.e., for publication in journals) non-compliant research should be considered more credible and useful in risk assessment and decision-making than studies conducted in accordance with validated test guidelines, conducted under GLP and submitted by the regulated community or others, or studies designed and conducted in accordance with Data Quality Objectives, as described in these Guidelines for EPA-supported studies.

Counter arguments have been put forth as to why/how these non-compliant studies may fall short of being fully adequate for risk assessment purposes. These include 1) Lack of access to the raw data to allow independent Agency analysis, 2) Insufficient documentation of the methods used, 3) Use of study designs that the Agency finds to be lacking in robustness in terms of amount of information gathered (e.g., ambient exposure or biomarker measurement at only one time point in a long-term observational human exposure measurement or epidemiology study; only one treated group in a toxicity study, 4) Peer review conducted in an opaque manner with no documentation of comments or adjustments made in response to the peer review.

Obviously, the Agency cannot force these "non-compliers" to reboot their research programs just to satisfy the Agency's needs or desires. However, the Agency could embark on an educational program (e.g., through sponsoring sessions at professional meetings and workshops or giving seminars at institutions conducting research of particular interest and value to EPA). The presentations could be designed to present and support the argument that basic research studies can be designed and executed in a manner which will satisfy both the researcher's basic exploratory curiosity and still be suited for integration into the risk assessment evaluation process.

Christopher W. Greene, M.S.

I would add that every URL in the document should be checked. I think EPA is currently revising/redesigning its website, so this might not be the ideal time to test for broken links.

Michael A. Jayjock, Ph.D., CIH

The following links in the document were of interest to this reviewer and found to be dead; that is, they either returned an error or put me into a web page that did not go to the indicated web site or have the document or information of interest.

In the references:

U.S. EPA. (2014c). Human Health Evaluation Manual, Supplemental Guidance: Update of Standard Default Exposure Factors. (Publication 9200.1-120). Washington, D.C.: Office of Solid Waste and Emergency Response, U.S. EPA. http://www.epa.gov/oswer/riskassessment/pdf/superfund-hh-exposure/OSWER-Directive-9200-1-120-ExposureFactors.pdf.

U.S. EPA. (2012f). Considerations When Evaluating Exposure Assessments. Washington, D.C.: Office of Pollution Prevention and Toxics, U.S. EPA. http://www.epa.gov/opptintr/exposure/pubs/consider_evaluate.pdf.

U.S. EPA. (2007e). Exposure and Fate Assessment Screening Tool Version (E-FAST). Version 2.0: Documentation Manual. Washington, D.C.: Exposure Assessment Branch, Office of Pollution Prevention and Toxics, U.S. EPA. http://www.epa.gov/opptintr/exposure/pubs/efast.htm.

U.S. EPA. (2004a). ChemSTEER (Beta Version). Office of Pollution Prevention and Toxics, U.S. EPA. http://epa.gov/opptintr/exposure/pubs/chemsteerdl.htm

U.S. EPA. (2001c). EPA Requirements for Quality Assurance Project Plans: EPA QA/R-5. (EPA/240/B-01/003). Washington, D.C.: Office of Environmental Information, U.S. EPA. http://www.epa.gov/quality/qs-docs/r5-final.pdf.

Özkaynak, H; Zartarian, V; Greim, H; Yu, H. (2011). Collaborative Project on Exposure Assessment. The 2nd International Conference on Risk Assessment, January 26-28, Brussels, Belgium. http://ec.europa.eu/health/risk_assessment/docs/ev_20110126_co19_en.pdf.

In Table 5-6: U.S. EPA (2011f) http://www.epa.gov/ncea/efh/pdfs/efh-complete.pdf\
http://www.epa.gov/risk_assessment/expobox/

Rebecca T. Parkin, Ph.D., MPH

It is notable that communication is discussed throughout this draft; especially in Sections 3.1.3, 3.4, 5.7, 7.2.8, 7.2.9, 8.4 and Chapter 9. Without an overarching, unifying definition of "communication" and other terms, however, these sections are not fully aligned. The point has already made about the importance of clarifying the term "communication" to be used in all chapters.

Similarly, uncertainty and variability (especially Chapters 3, 5 and 8) occur in several chapters. These important terms also merit a focused review to ensure that they are defined and presented comparably throughout the draft.

Executive Summary: This descriptive summary provides a clear statement of purpose and indicates that it updates several earlier EPA documents. The text identifies which topics are included and which are excluded from the *Guidelines*; e.g., one exclusion is high-throughput exposure assessment, which nonetheless is discussed in Chapter 6. This discrepancy needs to be corrected.

Chapter 1: In the overview, EPA's mission and exposure science are described. A list of past EPA documents is provided; the *Guidelines* are intended to update and supersede all of these. Further, the *Guidelines* were written for use across all parts of the Agency.

Both the Executive Summary and Chapter 1 indicate that non-occupational settings are the focus of the G*uidelines*. However, occupational issues are included in several chapters (e.g., Chapters 2-5 and 8), seemingly in conflict with the earlier exclusionary statements. If occupational exposure concerns are part of this document, even if they are not the focus, then edits are needed to clarify that inclusion. If they are not intended, then mentions of occupation in several chapters need to be reconsidered.

References: Some references were found to link to material which did not match the text or cited title; some of these problems are noted in the text above and III below. A number of links were broken during the August 2016 review of this document. All outdated links need to be corrected close to the time of publication.

P. Barry Ryan, Ph.D.

I have included pretty much everything I wanted to in earlier comments. Please note specific comments given below as they get too many of the details of the discussion presented at the meeting.

Alan H. Stern, Dr.P.H., DABT

See specific comments.

Clifford P. Weisel, Ph.D.

See specific comments.

V. SPECIFIC OBSERVATIONS

Paloma Beamer, Ph.D.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
4	1st	On the bulleted list not entirely sure if the difference between "key concepts and definitions for exposure science" from "concepts for exposure assessment" would be evident to those conducting traditional assessments.
9	Table 2-1	Add "stressor"
11	1st	Bioavailability of metals from soil is also affected by the significant pH changes along different parts of the GI tract
14	1st	Not only does biomonitoring only reflect aggregate exposures, many times a biomarker may disproportionately reflect certain exposure routes or pathways. For example, pesticides are more likely to be metabolized and excreted in urine if they are ingested and undergo first-pass metabolism versus those that are inhaled or dermally absorbed and end up in adipose tissue as the parent compound.
17	Last	When "inhalation exposure is assumed to equal dose" is this "uptake dose" or "intake dose"
18	Last	Need a better description of the different mechanisms of dermal exposure. Also need citations for the statements regarding contributions gases and aerosols.
19	3rd	Calculating dermal dose as a fraction of chemical that penetrates the surface barrier. This is very much a simplification that can be misleading and needs some clarification since "% absorbed" is dependent upon the initial loading (i.e., denominator). Many times this initial loading in dermal dosing studies (where most of these values comes from) is very high and not realistic. By inflating the denominator the overall "fraction" is reduced and may result in a gross underestimate. It is better and more appropriate to use models that take into account rate of diffusion, of which there are several simple ones.
25	Figure 3-1	Item 3.4 "Communication Strategy" is very important and should have more weight and not just be an after thought
26	Bullet list	Should add: "ensuring that the exposures being assessed are relevant and important to the affected communities"
27	Last	Project team needs to have representatives of the affected communities
30	First	Open and transparent dialogue with the community is necessary to make sure that the exposure pathways are being appropriately characterized for the affected community

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
31	Second	It is important that it is acknowledged that "EPA recognizes that the community could be aware of unique activities" impacting exposure… but the way this is presented it seems like an after thought.
33	Section 3.2	Problem formulation needs to address the "risk perceptions" of the affected community, otherwise how do you know if you will answer their questions?
37	Section 3.3.2	Are "environmental scenarios" and "exposure scenarios" the same thing? Because environmental scenarios are not discussed anywhere else.
40	Box 4-1	Should add Executive Order 12898 Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations
41	Box 4-2	Is the 2008 Child-Specific Exposure Factors Handbook not included because the 2011 EFH incorporates all of it? (Same comment for Box 4-3)
42	Bulleted list	Income is the #1 predictor of life expectancy across the US, consider including it as a sub-bullet (Chetty etl al., http://www.ncbi.nlm.nih.gov/pubmed/27063997). If necessary for space, can combine the two bullets on fish consumption.
43	Last bullet	Add chronic stress and exposure to violence
46	Figure 4-2	Figure is blurry and hard to read. It is also not clear if this is for US populations or for the world as a whole. Consider adding "Hobbies" such as arts/crafts, fishing and hunting.
47	Section 4.3.3.	Special considerations should also be considered for pregnant women and women of child bearing age
48	Table 4-2	More clarification is needed on how the potency adjustment should be used for lifestages. Is this applied as part of the "exposure assessment" or as part of the "risk characterization" in a risk assessment? It is important for exposure assessors to be aware of this, but the clarity is needed so that it is emphasized not to apply this potency factor at both stages.
49	After Box	Clarify what is meant by advisories
50	First bullet	In addition to IRB, many exposure assessments will require tribal resolutions, possibly at multiple levels. These can take months to get and should not be underestimated or underappreciated.
50	Last Bullet	About self-reported data needs to be reworded. This statement could be considered culturally insensitive as it is currently worded. Why would tribal members be any less reliable than the rest of the public?
51	Box 4-5	Add Lifeline C-BAS risk assessment model. It was specifically designed to use with tribal populations and contains many existing exposure factor databases for specific tribes.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
		Tribal Lifeline was included but needs to be updated to the current names.
52	Section 4.3.6	Perhaps include immigrants and refugees in this discussion too
57	Last Paragraph	It is great that EPA has so many GIS tools for examining EJ issues. It would be very helpful to have these tools listed as bullets or in a table with their differences and purposes highlighted.
50	Models	Add Lifeline C-BAS (i.e., Tribal Lifeline)
61	1st Paragraph	What is meant by "health survey and study output"?
71	3rd section	Is there any statistical criteria that should be used to determine if data sets can be combined?
72	1st paragraph	Could a list of legislative mandates be provided? Not all exposure assessors have a legislative mandate but it would be helpful to know which ones there are, in case they are pertinent.
80	Last bullet on page	How are exposure point concentrations defined and calculated? For those exposure scientists not involved in regulatory decision making, this is not clear. More guidance and referral to the appropriate documents would be helpful. If these are different by legislative mandate, than a list of those would also be helpful.
82	Bulleted list	Add a bullet for how the environmental data was analyzed. For example, you can get different concentrations of analytes in soil depending upon the sieve size used, or if the sample was ground. Similarly, they type of acid used can also result in different findings (e.g., nitric, hydrofluoric)
84	Table 5-4	Another important "typical measurement objective" is to determine if certain population has higher exposures than the general population. If they do, this can warrant the often times more expensive study to then disentangle exposure pathways by route and source.
88	Bulleted list	This section is confusing. Sub-bullets may help break it up and organize it so the hierarchy is more apparent.
95	Table 5-6	Do links for HEDS and NHEXAS work? Consider adding state tools and data sets to. For example, the pesticide use databases that are only available in six states.
107	2nd paragraph	The following sentence is odd and confusing… "Screening-level exposure assessments that use screening-level models are developed routinely in certain EPA programs."
108	Figure endnote	Add space after "al."
110	Footnote	Should this be "chemical concentrations in environmental media"?
111	Box 6-3	Any references for guidance on fitting distributions to data?
112	4th line	Should say "reasonably constant over time"

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
113	1st paragraph	The sentence that starts "Statistical models such as regression models…" is very important. However, it is confusing where it is placed in the paragraph because it seem like the following bulleted list of models are "statistical or regression models" rather than physical-based models.
114	6th line in last paragraph	Should be… hazardous "air" pollutants
116	First two bullets	Not clear what is meant by "demographic data" or "survey statistics" in this context. Perhaps provide some specific examples or refer to a table or box of examples?
116	Last paragraph	I'm assuming that the description here of the "microenvironmental method" is the same as the "microenvironment analysis" on page 111. It would be good to use consistent terminology. Could an example of the 2nd approach be provided?
117	3rd paragraph	The sentence beginning "Chemicals or their metabolites commonly…" is confusing as written.
118	1st paragraph	It would be good to provide an example of PBPK models used in children to successfully estimate biomarkers. It is important for people to realize that children are not just "little adults" but that all of the physiological parameters are very different because the body is still developing. Each one needs to be considered. It would also be good to highlight an example of how this approach can be used to assess contributions of multiple chemicals to the same non-specific metabolite.
119	2nd paragraph	Creatinine should also be discussed in Chapter 5 with this level of detail, in case those exposure assessors do not read Chapter 6. However, although creatinine is the most commonly used measure there is a host of problems with it as documented in the literature. Specific gravity is being increasingly used, but it is not clear how this would affect model estimates and comparisons.
119	3rd paragraph	First-order elimination rates are still considered pharmacokinetic data, not toxicodynamic data. Toxicodynamics are the direct interactions with a biological target that lead to functional or structural changes and the toxic effect. Pharmacokinetics have to do with changes in concentrations in tissues over time as a function of ADME.
125	1st paragraph	What is the benefit of using these more complicated sensitivity analyses and stepwise regressions?
133	3rd paragraph	This is an example of where it is not clear who the audience is. Is it just for EPA scientists? Or are they the only ones that "endeavor to apply the most currently scientifically valid approaches"?

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
135	3rd paragraph	Consider having a paragraph break at "In addition to environmental samples…"
142	Box 8-1	I'm not sure what the authors mean by the "laws of mathematical statistics and of Monte Carlo analysis."
148	Bullet list	How will uncertainty analysis be communicated to community members?
150	Figure 8-2	This figure is too sophisticated. There need to be less use of acronyms and they need to be better defined within the text.
167	Table 9-1	It would be helpful to also have "good examples" not just the "examples". What would be a better way of saying or demonstrating, "The chance of one having an exposure of more than 50 ppb is about 1 in 100"?

Nicole Cardello Deziel, Ph.D., MHS

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
32		Link not working properly *Public Participation Process for Registration Actions* website. U.S. EPA. http://www.epa.gov/pesticides/regulating/public-participation-process.html
41		Link incorrect http://www.epa.gov/risk/expobox/index.htm.
47		Link incorrect http://www.epa.gov/swerrims/riskassessment/sghandbook/index.htm
62	Table 5-1	Why include workers if this is non-occupational
16		Typo floating ", respectively"
181	This should be replaced with the second edition from 2015	Nieuwenhuijsen, MJ. (2003). Exposure Assessment in Occupational and Environmental Epidemiology. Oxford, U.K.: Oxford University Press.
		Check all links

Penelope A. Fenner-Crisp, Ph.D., DABT

Page	Paragraph	Comment or Question
xii xiii xv 20	P2/lines 1-2 P2/lines 1and 19 P3, line 1 P4, line 1	"Guidelines" is a plural noun, so adjectives and verbs associated with the word should also be plural "...Assessment, these Guidelines for Human Exposure Assessment are designed to aid.."
xii	P2/lines 5-6	"It is not a detailed instructional manual." Maybe not, but it should provide directions on how and where to find such detailed instructions for each area/program in which the Agency does exposure assessment.
xiv	P2/line 4	What is status of update of Cumulative Risk Assessment guidance? Might want to mention that it is underway, if it still is.
6	Figure	It's hard to read the words in red on grey and white on orange, even if you enlarge the page to 150%.
12	P2, lines 5-9	Yes, it would nice and preferable to have route- or medium-specific data when conducting a route- or medium-specific exposure assessment. But, it should also be acknowledged that sometimes one has to do route-to-route extrapolation or medium-to-surrogate extrapolation because the preferred data do not exist and an assessment has to be done anyway.
13	P5, line 4	"regulatory or statutory requirements" aren't the only factors that impact the approach and methods for exposure assessment. Add to those the availability of exposure mitigation technologies, their cost and political and societal considerations.
16	P2, lines 1-7	For FQPA purposes, OPP's working definition of "aggregate" exposure is somewhat narrower than this one. They assess food and drinking water as direct oral exposures, plus non-occupational exposure that is limited to residential use exposures (indirect oral, dermal, inhalation routes)
16	P3, 1-3	FQPA mandates that EPA consider "the cumulative effects of such residues [of the pesticide under evaluation] and other **substances** that have a common mechanism of toxicity." In reality, this would include non-pesticides, but OPP managed to redefine "substances" to be only other pesticides. Strict adherence to the mandate would have been an unmanageable option—too resource-intensive and time-consuming to do the necessary analysis.
17	P4, line 4	Has the Draft Protocol ever been finalized as such? Or, has it been integrated into the SHEDS-Residential model?
20	Box 2-1	OPP also has guidance on Revised Risk Assessment Methods for Workers, Children of Workers in Agricultural Fields, and Pesticides with No Food Uses-2009. Available at : https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0889-0002
20	Box 2-1	OPP also has tools/methods for conducting occupational exposure assessment for mixers, loaders, handlers, applicators. Cite them here,

Page	Paragraph	Comment or Question
		too.
24	P2, line 2	Hyperlink in paper did not go straight to HHRA Framework. This one did: https://www.epa.gov/sites/production/files/2014-12/documents/hhra-framework-final-2014.pdf.
29	P1, line 4	FQPA uses the phrase "mechanism of action." OPP reinterpreted it to mean "mode of action," so as to be consistent with the principles that were being developed around MOA in the cancer risk assessment guidelines.
31	Box 3-2	Add hyperlink to the webpage for Public Involvement Policy and Related Documents.
32	P2, line 4	Add "by external experts" after ""…will be peer-reviewed…."
33	P3, line 1	Change "population" to "population(s)"
34	P3, line 8	Change "assess" to "assessing"
39	P1, lines 14-16	"Tools and methods are available…… and are being applied, particularly by academic researchers and some state agencies." The way this sentence is written suggests that EPA is developing all these tools and methods and they are being used only by outside parties and not EPA. I doubt if that is the intended message. Revise to clarify.
40	Box 4-1	Revise title to read "Provisions of Presidential Executive Orders." No Agency policies are included here.
40	Box 4-1	Language summarizing contents of E.O's 12898 and 13045 should capture the wording of the E.Os more faithfully. Revise from: **12898**- "1. To the greatest extent practicable and permitted by law, and consistent with the principles set forth in the report on the National Performance Review, each Federal agency shall make achieving environmental justice part of its mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of its programs, policies, and activities on minority populations and low-income populations…." " 2. Development of Agency Strategies. (a) ~~Except as provided in section 6-605 of this order, each Federal agency shall develop an agency-wide environmental justice strategy, as set forth in subsections (b)-(e) of this section that Identifies~~ Identify and addresses disproportionately high and adverse human health or environmental effects of its programs, policies, and activities on minority populations and low-income populations. The environmental justice strategy shall list programs, policies, planning and public participation processes, enforcement, and/or rulemakings related to human health or the environment that should be revised to, at a minimum: (1) promote enforcement of all health and environmental statutes in areas with minority populations and low-income populations; (2) ensure greater public participation; (3) improve research and data collection relating to the health of and environment of minority populations and low-income populations; and (4) identify differential patterns of consumption of

Page	Paragraph	Comment or Question
		natural resources among minority populations and low-income populations……." **13045**-"(a) shall make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children; and (b) shall ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks.
40	P2, line 3	Why just "especially aggregate exposure"? Why not cumulative, as well?
41	Box 4-2	Revise to read "Recommends changes in policy and risk assessment practices to better reflect children's health and exposure factors in evaluating exposure to pesticides in food and water." Hyperlinks to http://www.epa.gov/osp/tribes/priorities.htm. and http://www.epa.gov/risk/expobox/index.htm. don't work
44	P1, lines 13-15	"During the planning and scoping process (Section 3.1), an exposure assessor considers whether establishing dialogue with toxicologists/health scientists is needed to consider specific "windows of susceptibility" in an exposure or risk assessment." This should not NOT be an option. It should be obligatory in every case.
47	Last line	Hyperlink http://www.epa.gov/swerrims/riskassessment/sghandbook/index.htm). Doesn't get me there.
63	P2, line 4	Should be EPA 2012f, not EPA 2012i. URL in reference section for EPA 2012f does not work. This one does: https://www.epa.gov/sites/production/files/2015-09/documents/consider_evaluate.pdf
63	P2, line 6	Is EPA 1992b the most current "take" on this topic or has it been updated?
63	P3, line 2	Should "need' be "could?"
63	P4, Question 1	I'd want to know about the nature/kind of data available as well as its quantity
63	P6, Question 2	I'd want to know if the methods had been validated before being adopted
70	P1, line 9	I'd insert a sentence reminding the reader/user that selection of appropriate method(s) may be determined or dictated by Program-specific guidance and practice
76	Box 5-2	Bounding estimates are used "to determine whether more data and information are needed to evaluate other exposure pathways or to refine the exposure assessment." MEI: Does every Program/Region use this term?
77	P2, line 2	Add sentence reminding reader that "They may, or may not, be the same as those found in the Exposure Factors Handbook."
78	Last line	"EPA 2012i" should be "EPA 2012f"

Page	Paragraph	Comment or Question
79	P4	Somewhere in this section there should be a discussion of the criteria to be used when deciding "enough is enough," that is, when is the amount and type of data (to be) collected just enough to conduct the assessment at the desired level—"not too little, not too much, just right."
80	P1, lines	" EPA programs have developed many guidance documents and compiled resources that detail the specifics of planning and implementing a sampling program." Make sure they are all cited in the document somewhere, in lists, tables, boxes, reference section, etc.
102	Table 5-6	Add two more databases to list of those compiled by other federal agencies: 1) USDA's Pesticide data Program https://www.ams.usda.gov/datasets/pdp 2) FDA CFSAN Office of Analytics and Outreach Total Diet Study http://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/default.htm
128	P1, lines 1-6	Strike the second sentence (lines 4-6, as it is a repeat of the first sentence (lines 1-4.)
136	P1, last line	Revise to read "….Sciences Institute's ~~risk assessment~~ framework for children's risk assessment (Olin and Sonawane 2003).
141	P4, line 1 P6, line 1	Flip the "for" and "both." Replace "This" with "These."
143	Table 8-1	To clarify, revise to read "Use of a small sample of individuals to estimate risk to all exposed workers"
145	P3, last line	Change "this" to "these."
146	Table 8-2	"Will using a ~~combined~~ different dataset be a problem?" seems to be a better match for the question asked in the Questions/Approaches box
147-148	Section 8.2.1 List of questions	Recommend re-ordering and editing as follows: • Will a quantitative analysis improve the assessment? • What are the major sources of uncertainty? • What are the major sources of variability within the individual/lifestage/group/population? • Have the weaknesses and strengths of the methods involved been evaluated? • How will the uncertainty and variability analysis affect the regulatory decision? • Will a quantitative estimate of uncertainty improve the decision? • Will a quantitative estimate of the variability of a specific exposure parameter improve the decision? • What level of effort is warranted for this project? • What time and resources are available for conducting an evaluation? • ~~How available~~ Are the needed skills (e.g., statistical expertise) and experience ~~needed~~ available to perform the analysis?

Page	Paragraph	Comment or Question
		• How will the uncertainty analysis be communicated to the risk managers/decision makers and stakeholders?
153	Section 8.3.2, P1	I would add a sentence at the end of this paragraph to read "The decision to exclude an exposure scenario from an assessment needs to be clearly communicated to the risk manager/decision maker and stakeholder(s)."
153	P3-4	For clarity's sake, I would recommend moving the first two sentences of P4 up to the beginning of P3 to read "The basic process for conducting a screening-level analysis ~~includes:~~ uses a deterministic approach. This approach entails developing a point estimate of exposure and using point estimates of toxicity to calculate a hazard quotient (noncarcinogenic effects) or risk level (carcinogenic effects) or margin of exposure. This process includes:…..[the four bullet points]"
165	P1, lines10-11	"~~This~~ These Guidelines for Human Exposure Assessment ~~is~~ are not intended……."

Christopher W. Greene, M.S.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
many	many	I think the standard practice in U.S. English is to use the Oxford comma for lists, but this document almost never does. It's not required, but in my opinion it improves readability, especially when each item in the list contains many words.
many	many	The document uses brackets [ ] inside parentheses ( ) when they are nested. This looks strange to me—I would just use parentheses.
4+	Chapter Heading	All chapters should start on an odd-numbered page so that they appear on the correct (right-hand) side when printed.
4	2.1 para 2	"the committee." What committee? Does this refer to the NRC?
5	Figure 2-1	Upper left corner. Chemical, Biological, Physical, and Non-Chemical. What is non-chemical? Is that an "other" category that is also not biological or physical? What's an example of this? At first I thought it meant stressors like noise or emotional stress, but noise could be considered physical, and stress biological.
5	Line 9	exposure—here refers to exposure *at the boundary of the body*; you might want to specify that.
5	bottom	"actions or events might be sources of stressors…" Actions or events might also *be* stressors themselves.
5	bottom	What are "changes in human and natural factors?"
6	Figure 2-2	Circle says "sources." Sources of what? Define "Environmental Intensity." Do the various colors (sometimes matching, sometimes not) mean anything?

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
		What is the unlabeled box that surrounds "Stressors" and "Receptors?" What is the difference between a source and a factor? What does an arrow mean in this framework? Does it represent influence or steps in a process? "Dynamic System" at the top: Is that the only part of this that is dynamic (and items to the left and right are not dynamic?) What does that mean?
6	2nd para	"Exposure science is developing methods…" I suggest changing this to indicate that *scientists* are doing this, not science itself.
6	last para 1st line	Focus is on the receptor rather than the sources. However, some sources, e.g, drinking water and food, are inherently human-focused. Also, contrast this statement with Section 2.3.2 at the top of page 13.
7	2nd para 1st line	The term "lifestage" is used here (and elsewhere) to describe a cohort of people, not a stage through which a population passes. Is this a common usage? I would have used it differently: For example, to me, *infancy* is a lifestage; *infants* are not a lifestage. So receptors can be an individual or population, but not a lifestage.
8 9	2.2.1 2nd para Table	Exposure period and exposure duration. I think something should be done to better explain the difference between these two concepts.
9	Table	Under "Exposure": Does *receptor* in this table cell refer to the person or an individual organ/system? The definition of *receptor* in the same table refers to a biological entity. Can that be an organ? A cell? A DNA molecule?
9	Table	Some items in this table may benefit from a statement of what units are commonly used to express them, e.g., mass of chemical per unit body weight per unit time, etc. This would help given that (as the text states on p. 10) different disciplines use different terms.
10	Table 2.2	Units for some of these concepts would help differentiate between dose and response.
10	below table	"Uptake involves crossing an external exposure surface…" Based on definitions set out in the nearby tables, I wonder if this should say "an inner exposure surface…"
10-11	bottom 10, top11	Is there a citation for the statement on the bioavailability of metals? (Or is it the EPA 2007l mentioned in the statement about lead?)
11	top	Delivered dose: is "amount" expresses in mass, mass per unit body weight, or mass per unit BW per unit time?
11	top	Transported "to the location where the adverse effect occurs." Is this always so? Can a chemical's toxic effect at one location in the body cause an adverse effect elsewhere? (I suspect that it can, but I'm not a toxicologist.)
12	top	Note for the figure should stay on previous page.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
12	1st bullet	Define "hazard."
12	2nd bullet	Explain the difference between *toxicity* and *potency*.
13	2.3.2 point 1	"Exposure-response" is a new concept introduced here. This might require some explanation and contrast with dose-response.
13	2.3.3 para 1	The last sentence is a good synopsis of the value of exposure assessment. This could be developed further.
14	1st para	2nd to last sentence. Note also that biomonitoring data aggregate exposures from all routes and pathways, *and not always in an equal or proportionate manner*, i.e., some exposure routes may manifest themselves more strongly in the blood/urine/etc. than others.
15	After bullets	Scenario-based approach and population-based approach: Can the text provide example(s) of each? i.e., "people who work in paint factories." "Children 3 to 6 years old." etc.
16	1st line	Does a probabilistic approach "depict" uncertainty? Could change to say it *accounts for* uncertainty or *addresses* uncertainty.
17	2.4.1	Inhalation exposure is assumed equal to dose—Where? At the lungs? At the mouth/nose?
18	1st line	"Complicated"—but earlier in the paragraph the text says that in many cases dose is simply assumed to be equal to exposure.
18	2nd equation	If C_{ing} can be stated as mass of chemical per volume of medium, the IR term would have to be volume per time, not mass per time, for the units to work out properly.
19	Equation	How is "contact" defined? For example, if a puddle of liquid is held in a cupped hand, what part of the mass of the liquid is considered to be in contact with the skin?
19	center of page	I suggest adding an equation showing the use of a permeability coefficient. Maybe also some discussion on film thickness on the skin and how that translates to an external dose at the skin surface.
26	Figure 3-2	What does an arrow represent: flow of information through the process, or influence of one element upon another?
27	3.1.1 1st para	Good opening paragraph. I suggest moving the short and succinct final sentence to the beginning of the paragraph.
27	3.1.1 2nd para	This paragraph could use some concrete examples: What does this sort of thing look like in real life?
27	3.1.1 2nd para	Last sentence: I suggest changing text to read: …fate and transport properties, and routes of exposure;…
28	2nd para 1st line	I suggest changing *need to be* to read *should be*.
28	3rd para	Can the text provide examples of each type of assessment (Screening, lower tier, complex)?
28	last line	"are required." When done by whom? This gets to the question of who the intended audience is for this document.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
29	3.1.2	An additional topic should be added to the list: Multiple exposure sources to a single chemical. This topic seems to come up a lot and is an important part of risk management.
29	3.1.2	Suggested rewording: "It is essential that exposure assessors be cognizant of these overarching themes so that…"
33	3.2.1 1st line	Suggest changing *An important aspect* to *One important aspect*.
33	3.2 1st para	There is a reference to Microbial RA guidelines, but Chapter 1 states that this is outside the scope of the document.
34	1st line	"assessments need to… understand.." An exposure assessment doesn't *understand* anything; I suggest changing either the subject or the verb in this sentence.
34	1st para	Why only assess exposure situations that affect the most susceptible population?
34	1st para	The part describing dialogue with toxicologists and health scientists is important and I'm glad it was included here. If possible, this should be expanded at least to a paragraph in this section.
34	end of page	This whole section (3.2.2) is good, but would benefit from some concrete examples. Maybe link to some existing conceptual model descriptions.
35	2nd para after bullets	This paragraph is a good start to addressing the lack of examples that can leave the reader wondering, "What does one of these look like in real life?" A paragraph like this should be included in other parts of the document where this clarification is needed.
36	2nd to last line	What is an "exposure area?"
36-37	Sec 3.3.1	Any advice for using pre-existing data (like published research, etc.) when you don't have control over the study design?
36-37	Sec 3.3.1	What constitutes a "data gap?"
38	last line	This is the best example in the document of a statement that makes the reader wonder about the intended audience for this document. Does EPA expect and encourage non-EPA organizations/entities to use this document?
39	1st para	Other hyperlinks in the document show the URL, but these do not.
39	2nd para	"assessments involving potentially vulnerable populations." Don't they all?
40	4.2 1st para	"randomly." By this, does the author mean "equally/evenly?" Also, exposures can also vary throughout the population. I suggest changing the 1st sentence to read, *"Environmental exposures and health risks are not distributed evenly across the landscape or throughout the population. Rather, they are concentrated among…"*
41	Box 4-2	The Expo-Box link redirects to the main page, epa.gov/risk. Change to https://www.epa.gov/expobox.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
		I didn't check the other links.
41-42	all	The definitions here seem a little muddled. At the start of the section, vulnerability and susceptibility are presented as distinct concepts, but later, the latter is a component of the former. Then, on page 42, the text jumps from two concepts (vuln. and susc.) to four properties of vulnerability, one of which is a particular sort of susceptibility (differential susceptibility.)
42	Figure 4-1	What are the two boxes? Is the left one vulnerability, and the right one susceptibility? How do the boxed items relate to the diagram behind them?
42-43	2nd bullet	I appreciated the inclusion of some real-world examples here. If possible, this should be done a lot more in the document.
43	line 2	Is there a standard sort order for citations? This list is not oldest-to-newest or newest-to-oldest. (Are they all done alphabetically?)
43	after bullets	The first sentence of this paragraph is repeated from page 40. I suggested an edit there—see above.
43	4.3.1	See comment above for page 7, definition of *lifestage*. (Feel free to ignore these comments of this use of the word *lifestage* is consistent with EPA practice.)
44	4.3.2 1st para	In the quotation of EO 13045, I suggest changing the colon to an ellipsis (…)
45	line 3	"the relationships between maternal and fetal exposures…" You may want to note that all of this is highly chemical-specific.
45	2nd para	Good discussion of activities. You may want to mention that each of these can vary greatly over time, and are not simply "on" or "off."
46	Box 4-3	No mention of the Child-Specific EFH? Or was this superseded by the 2011 EFH?
46	Figure 4-2	There are a lot of important activities that are not included in this chart. For example: bathing; hobbies; use of paint, glue, etc.; riding in buses; using cosmetics/other personal care items; dental sealants; swimming; fish consumption.
46	Figure 4-2	From page 43, childhood includes the prenatal period. Any insight to add to this chart?
46	Figure 4-2	In the legend: "Activity most likely occurring." Does this mean that most people in the age group are doing the activity, or that a given individual, if they are going to do the activity at all, is probably doing it by this point in life?
47	4.3.3 1st para	Thank you for including examples here.
47	bullets	The bullets for "other lifestages" only discuss the aged. Is childhood a lifestage? It is not expressly listed as such, only as a "sequence of lifestages." (p. 43.) Can lifestages overlap?

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
47	4.3.4	Good opening paragraph. Integrating exposures over a lifetime is an important concept and also has applications in the use of exposure factors such as water intake.
47	4.3.4	End of first paragraph: fetal is part of childhood, according to the definition provided in 4.3.1, paragraph 1.
47	4.3.4	Fetal, childhood, etc. are called "age groups." Is there a reason these are not called lifestages? Is a distinction being drawn here?
49	2nd para	"Each tribe follows unique traditional practices…" This paragraph paints with a rather broad brush. Text should note that individuals within a tribe may vary greatly in their adherence to traditional cultural mores. The examples given (basket making, sweat lodge ceremonies) are not "unique" to any one tribe.
49	3rd para	"The percentage subsistence and frequency…" Percentage of what? Frequency of what?
49	3rd para	Suggest changing *fish or other game* to *fish and game*.
49	para below box	Some citations for the statements in this paragraph would help direct the reader to more details.
49	para below box	"Exposure scenarios… need to account for sustainability…" What would this look like in practice? If exposure is occurring, it is occurring regardless of the sustainability of the practice.
49	1st bullet	*Some* tribes are tied to fixed land bases; see text at bottom of p. 48.
49	2nd bullet	Re-word the first sentence. How are data "gathered potentially?"
49	2nd bullet	What are "the issues of informed consent?" Please elaborate.
49	2nd bullet	"Tribes need to be made aware…" Caution, this could come across to some readers as patronizing. See comments under the charge question for this chapter.
50	2nd bullet	Science is NOT an exclusively western construct. I recommend rewording this.
50	2nd to last para	"EPA mandates…" For whom?
51	2nd to last para	"…in Indian country." Exposures particular to native peoples may be relevant outside the bounds of the reservation system, such as with Native populations that are urbanized.
52	4.3.6 2nd para	Last sentence. What did they find?
53	1st line	Anything to report on differences in consumption between generations, i.e., first-generation immigrants and their children?
54	middle	"Reduced levels" implies they used to be more highly regulated. Should this be changed to "lower levels?"
54	last line	What is *sensitivity* in this context?
55	Box 4-6	Text says "X is _____." Something seems to be missing.
57	1st para	How can this information be applied within the document's framework of exposure assessment? Based on Chapter 1, this may be

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
		outside the scope, but if possible, something should be said about application.
58	1st para	Is body burden defined anywhere? Are there other metrics as well? Body burden is not always a useful metric.
58	4.4.1	"locally unwanted land uses." Land uses that create exposure problems may not be "unwanted," due to a lack of awareness of the hazard and the potential of benefits, such as jobs, tax revenue, etc.
59	4.4.5, line 2	"pollution exposures." Any reason not to say "chemical exposures?"
61	2nd bullet	Suggest writing acronym reference as "quality assurance/quality control (QA/QC)"
62	Table, last row	What is "naturally occurring food" as distinguished from locally grown food, fish, and game? Would this be things like wild berries and mushrooms?
63	top of page	Is it possible to run this process backwards, i.e., to scope an exposure assessment to fit the quality and quantity of available data? This is potentially useful when assessing chemical exposure with tight budget and/or time constraints.
63	3rd bullet	These bullets (paragraph above) are good. The 3rd bullet: Good question, but the answer can be subjective.
63	1st set of bullets	Can this section address the use of geographical surrogate data, i.e., data gathered at another location with similar exposure concerns?
66	Box 5-1	As in a couple of other areas, many of these links do not show the URL, but a hyperlink. I think the document should do it one way or the other, not a mixture.
67	middle of 1st para	"the team considers the benefits of the additional information against the cost…" Can the authors give an example of this analysis? (no long description needed, maybe a link to a report where this was done.)
67	last para	Can "secondary research" be defined? Is it the citation/application of an existing work?
70	5.2.2 first para	Detection limit, quantification limit, method detection limit, reporting limit. Can these be defined briefly? Does everyone use consistent definitions of these terms? If this document is aimed at guiding EPA staff doing exposure assessments, you might consider formally defining these terms here.
70	1st bullet	Last sentence: is there a hard limit on the ratio of nondetects to total number of samples, below which substitution should never be used?
70	1st bullet	The DL divided by the square root of two is also commonly used.
71	line 3	I suggest not capitalizing the term *open source*.
72	5.3.2	"Biomarkers are…measures that can indicate exposure." Is the biomarker a *measure*, or a thing that *is* measured?
72-73	end 72, top 73	"Biomarkers record the concentration of the chemical or its metabolites in biological media…" Does this mean that if you have *x*

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
		concentration of biomarker *y* in your blood, you were exposed to *z* amount of chemical *c*? Why is the term "record" used? To me, that implies a series of points in time, when what you're really getting is sort of an integral of your past exposures, with the time parameters dependent on the chemical's behavior inside the body.
73	Figure 5-3	It would be helpful to define the terms used in this figure.
74*ff.*	general area	Although it has not yet been released in its final form, it might be good to mention EPA's ExpoFIRST here, or in another appropriate section. It functions both as a data source (referencing key tables from the EFH) and as a sort of screening-level model (in that it lets the user run exposure scenarios.) It may be released to the public before the Guidelines document is finalized, and if so, a link could be provided.
76	end	The Expo-Box link does not work. Remove the */risk* from the URL.
81	Table, Row 1	The terms ground water and groundwater are used throughout the document. I suggest using one or the other and being consistent, except when quoting another document.
81	Table, Row 4	Consumer products are included in the target media, so they should be mentioned in the column on sources—something on personal care products, household chemicals, and pesticides.
81	Table, Row 4	How are "Crops and Livestock" a source of data? I suggest rewording to be like the other items in the list.
85-86	Bullets	Is the Child-Specific EFH a good source to list here, or has it been superseded by the 2011 EFH?
102	Table 5-6	In the "not exhaustive" note at the end of the table, you might add that many states have environmental databases as well.
102	Table 5-6	2nd to last row: description of WQ Portal. You might add that the portal relies in part on STORET and USGS's NWIS database.
102	Table 5-6	You might also add that USGS does a lot of analytical work on "Contaminants of Emerging Concern"—PPCPs, etc., and a lot of this work does not appear in publicly available databases, but is in reports published by USGS.
102	Table 5-6	The Unregulated Contaminant Monitoring Rule (UCMR) project, editions 1, 2, and 3, provide useful drinking water concentration data that is both abundant and highly localized. It might be worthy of a mention in this table.
106	last row	The URL didn't work. Every URL in the document should be checked.
107	last para	Right after describing a continuum from simple to advanced model, the text says, "An example is… E-FAST." Where would E-FAST fall on the continuum of simple to advanced?
113	1st para	"processes in the source-to-exposure continuum." I suggest rephrasing this.

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Page	**Paragraph**	**Comment or Question**
113	1st para	I suggest adding a word: "The emphasis here is *on* physical-based…"
113	1st para	What does "physical-based" mean here?
113	2nd bullet	How does one get from concentrations to exposures?
113	last para	The text here gets a little bogged down; a diagram or table might help. Groundwater flow might include sorption and desorption; volatilization and dispersion in air may include inputs from a chemical moving from the liquid phase (water or wet soil) to air. Chemical processes may include hydrolysis and photolysis. Is radioactive decay a physical process or a chemical process?
113-14	end 113, top 114	Why are these two particular models mentioned here, while no water-centric models are mentioned?
114	last para	Can the text differentiate between SHEDS-Air and SHEDS?
115	2nd para	The assessor "links this information with individual or population exposures." This implies both the concentration information and the exposure estimates are pre-existing. How can this link be made if the assessor is in the process of estimating the exposures?
117	2nd para	Bolded text should be "Dose Estimation Models," based on the bullets on page 113.
117	3rd para, line 4	I suggest changing *is* to *function as* or *constitute* to address the plural noun *biomarkers* transitioning to the singular noun *tool*.
117	long paragraph	The sentence on the characteristics of a good biomarker repeat text from the top of page 73.
118	top	"Either the model used to predict the biomarker is flawed or the assessor missed sources and pathways of exposure to the chemical." How does model conservatism play into this sort of outcome?
118	Table 6-2	I appreciate the addition of this table showing real-world examples of forward and reverse dosimetry.
119	2nd para	"timing of the accumulation period and urine volumes…" How is this done? By taking the first urination upon waking in the morning?
119	center	A compartment "not physiologically defined…," such as volume of distribution. How is the volume of distribution defined, if not physiologically?
119	center	End of paragraph, "inherent assumptions." Such as? Does this mean assumptions such as linear responses, instantaneous mixing within each compartment, etc.?
119	last 4 lines	"Important to note, however, is that…" I suggest rewording this. It's a bit awkward.
119	last 2 lines	"…Reductions in uncertainty and increases in accuracy are not necessarily predetermined results." What does this mean? If it's just a way of stating that the desired outcome does not always occur, I suggest rephrasing the "not necessarily predetermined results" part.

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Page	**Paragraph**	**Comment or Question**
119	last line	"PBPK models are recommended to:" This is a bit awkward, and I suggest changing it to: "EPA recommends the following:"
120	para after bullets	"Prioritizing the need for animal testing." I wasn't sure what this means. Targeting chemicals for animal testing?
120	para after bullets	"other purposes." What does this refer to?
120	para after bullets	Last sentence suggests that a "possible increase in the uncertainty in the model predictions" is one of the things being "traded." But isn't this one of the things you are *getting*, not trading away, when you use a high-throughput model? It might be better to describe this not as a trading transaction, but gaining certain qualities while sacrificing other qualities—a subtle difference, but perhaps clearer.
121	long para	2nd line: "data (e.g., other model predictions…) Do model predictions qualify as "data?"
121	long para	3rd line: Suggest changing "quality assurance (QA)/quality control (QC)" to "quality assurance/quality control (QA/QC). However, note that this abbreviation has already been defined; see page 61.
122	Figure 6-3	The words "Select Model" are not bold; all if the other text is bold.
122	Figure 6-3	What's flowing in this flowchart? It seems like some of the arrows represent steps in a process, some represent the flow of information, and some represent influence. What is the difference between a solid arrow and a dashed arrow? A thick arrow and a thin arrow? What are the brackets [ ] for? Are the problem definition and conceptual design one thing or two? If two, are both of them "hypothesis-based?"
122	6.3.1 (and others)	I suggest not hyphenating *risk management*. There are a few other instances with the hyphen in the document, but many more without it.
127	1st para	Can an "observational human exposure measurement study" include, for example, a study in which food items are sampled and analyzed?
127	3rd para	"the potential clinical significance of biomonitoring results has been established for relatively few chemicals." Can you expand on this? (i.e., significance for what purpose?)
128	2nd para	Remove extra spaces after the first sentence.
128	7.2	Citation list: perhaps it would help to provide a short (sentence-long bullet point or table entry) on each of these sources.
129	7.2.2	What is a "data element?" (also on previous page)
129	7.2.3 1st para	"power that the study can achieve." Does this refer to statistical "power," or something else?
129	7.2.3 2nd para	You might want to devise a different example on the topic of effect size; "subsistence" and "landlocked" are not mutually exclusive, and some landlocked peoples do consume fish.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
130	7.2.6	HEDS link is broken. This could be due to EPA doing a site redesign, temporarily(?) breaking some links.
140	whole page	The definition of *uncertainty* and *decision uncertainty* are a bit muddled on this page. In the first sentence, decision uncertainty is presented as a subset or an element of uncertainty. At the end of the second paragraph, the broadest term (uncertainty) is used as the definition of decision uncertainty *and* data uncertainty together, even though data uncertainty is a subcategory of decision uncertainty (per the 4th sentence of the first paragraph.) It's like saying mammals are a category of animal, but when talking about both dogs *and* mammals, the term "animals" is used.
140	1st para	Fifth sentence: not all of these are discussed in section 5.5 as stated.
140	last para	I suggest removing the hyphens from *risk management* and *decision making.*
140	whole page	How does parameter sensitivity fit into these definitions of uncertainty?
140	whole page	How do these definitions fit in with the uncertainty terms in Section 2.3.4?
141	2nd para after bullets	1st sentence refers to risk assessments. Is this the exposure assessment sections of risk assessment reports? Does the statement apply to exposure assessments as well?
141	8.1 1st para	"the lack of, incomplete or incorrect information." I found this awkward; the document should use parallel construction in lists.
141	8.1 last para	I had trouble parsing this list. Is it describing six types, or three, or two?
141	Box 8-1	Bullet 1. Does uncertainty here refer to both data and decision uncertainty, as mentioned on page 140?
141	Box 8-1	Bullet 1. I suggest using the 2nd to last sentence as the first sentence, and rewriting what is currently the first sentence.
142	Box 8-1	Latin hypercube is not defined, while Monte Carlo analysis gets its own bullet after being mentioned in a previous bullet.
142	end of page	This bullet seems "lost"—not near the others in the set.
144	Figure 8-1	Is this a frequency distribution? The horizontal axis indicates all the bars are results from the same sample. If so, the indicated bar isn't the mean, it's the maximum. If each horizontal division is 1, the mean is about 3.5. If it's a frequency distribution, the vertical axis should represent the number of times a given value was observed, and the horizontal axis would be the range of observed values; then the indicated bar would be the mode. Also, the title says this is about data analysis. Isn't it more about *measurement* uncertainty in the laboratory analysis of a *sample*?

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
145	8.1.1	1st paragraph: This subsection is about data uncertainty; are all the statements about "uncertainty analysis" and "sources of uncertainty" intended to be about data uncertainty, or a more general definition of uncertainty?
145	8.1.1	2nd paragraph: "natural variability:" same as variability, as defined on page 140?
147	8.2 2nd para	"Does one specific exposure scenario substantially contribute to total exposure?" In this sentence, does the writer mean *only* one scenario contributing most of the exposure (a single predominant exposure source)? I just wasn't sure what "substantially contribute" means here.
147	8.2.1	1st bullet: Can you provide examples of when a quantitative analysis would or would not improve an assessment?
148	3rd bullet	How is this different from the first bullet on the previous page?
149	8.2.3	This section might also refer the reader to the material in Section 8.4.
160	9.2.1	End of first paragraph: the list doesn't use parallel construction (noun, noun, verb.)
160	9.2.1, last paragraph	"Regulatory decisions are policy decisions." Is a regulatory decision a finding that a standard has been violated, or is it a decision that "this is the standard that must be followed?"
161	whole page	I thought this page was well-organized; presents principles, then elements of an exposure characterization.
161	1st para	"Policy judgments:" different from "policy decisions" from previous pages?
161	last line	Clarify this bullet. "appropriate for the intended exposure characterization." Does this mean appropriate for the intended audience?
163	9.2.3 2nd para	"Assessors need to consult with their programs." This echoes a similar statement in a previous chapter, and to me, it comes across as very EPA-centric. I suggest rewording this.
164	4th para	"Whether using graphics or a numerical table, the item needs to be self-explanatory; capable of communicating the critical information without reliance on the narrative to explain the main message." This principle should also apply to this *Guidelines* document.
165	9.3.1	1st sentence: is this statement intended to apply specifically to communication with risk managers/decision makers, or all audiences?
165	9.3.1	Last sentence: *nonscientific aspects*. Would this include political aspects? What other aspects?
165	9.3.2 2nd para	Example at the end of the paragraph: How were these communicated, and how can this inform new exposure communication challenges?

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
166	bullet list	This is a good list, and many exposure assessors can recall seeing some of these attitudes from the media. However, as one of the other reviewers wisely noted during the peer review panel discussion, it is a bit one-sided. There are many examples of journalists who strive to get the story straight and gain understanding of the science.
166*ff.*	9.4	I think there needs to be some discussion here on how to make documents accessible to the disabled. There are a lot of resources out there on how to make Word documents and PDFs work well with screen readers and other assistive devices, and many agencies and institutions mandate this to one extent or another.
166*ff.*	9.4	Perhaps something could be added here on providing information in languages other than English to audiences the might need it.
166*ff.*	9.4	I would also like to see something here on how to communicate low confidence, especially to a lay audience. This is dealt with a little in other parts of this document, but might go well in this section as well.
166	4th bullet	The first five words are in a different typeface than the rest of the document.
167	Table 9-1, 3rd row	I would like to see something on the use of "industry-funded" studies, which many in the general public view with skepticism, even though some such studies *can* be acceptable for use in exposure assessment projects.
167	Table 9-1, Row 7	"Balance a negative statement with three positive statements." This seems a bit odd for a rule, or perhaps I'm not understanding the concept. Shouldn't the number of positive and/or negative statements depend on the information being presented? Perhaps this could be explained further.

Michael A. Jayjock, Ph.D., CIH

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
1	1 para 2nd sent	The Agency needs to understand whether an agent might cause a health effect [under conditions of anticipated user] and how exposure to the agent could be reduced. Note: ALL agents will cause an adverse health effect at some exposure.
9	Table 2-1	Exposure point — The location **[in space and on the body]** at which the receptor comes in contact with the agent.
13	Section 2.3.2	What are the characteristics of exposure (e.g., intensity, frequency, duration, route[s] of entry)? The primary purpose of the exposure assessment is to estimate exposure or dose, which then is combined with chemical-specific [and time period-dependent] exposure-

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
		response or dose-response data (often from animal studies) to estimate risk.
13	Last para, 2nd sent	Direct (i.e., point-of-contact) methods measure [or model] the contact of the person with the chemical concentration in the exposure medium over an identified period.
18	Equation	Einh = inhalation exposure (mass per time) **[Over the duration of exposure]**
33	3.2.1 1st para 2nd sent	For a scenario-based approach, an exposure assessor defines a specific receptor of interest, usually because of a distinguishable characteristic or behavior that might predispose the individual/lifestage/group/population to a potentially greater exposure concentration or dose [or have greater toxic effect on the receptor at any particular dose]
35	bullet #6	Timeframes of exposures: What are the relevant timeframes—frequency, duration, intensity and overlap of exposure intervals [and their fit to the time-frame of available toxicological benchmarks]—for a stressor or mixture of stressors?
48	Table 4-2 last column header	[Cancer] Potency Adjustment (U.S. EPA 2005h)
61	1st para. 2nd sent	Possible data types include physical measurements of environmental and biological media, health survey and study outputs, location-specific or population-based activity information and scientific research findings. [and model input parameters].
105	4th para 2nd sent	Considerations include identifying population groups of concern; determining whether outputs need to be presented on an [hourly], daily, quarterly, yearly or multiyear basis; deciding on the number of prediction years (i.e., lifetime or shorter timeframes);
108	Last para, last sent	Screening-level models also can be used to determine if the potential for exposure justifies an in-depth evaluation of the problem by using a more sophisticated exposure model [or monitoring].
109	Fig 6-2	Single value output graph: Question: What is D in the abscissa? It appears to be an error
153	3rd bullet	Comparing the estimated exposure to[toxicology-based] screening values

Rebecca T. Parkin, Ph.D., MPH

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
2	3/1	"principal focus" is not appropriate. Focus is singular in nature, so there are no other foci possible. Perhaps the meaning here is more like "The *Guidelines*…are focused on human exposure to chemicals…"
2	4/1	"focuses primarily" is the same issue as above. Secondary foci are not possible. Perhaps "This guidance emphasizes the data…" would work here. Similar problems with "focus" were noted elsewhere in the draft but not recorded further in these suggestions. Please check for other irrelevant adjectives with "focus."
2	FN/all	This footnote is not clear. Does the second sentence mean that "stressor" would not be used in any chapter except #2 or only where the NRC used it? If so, neither is what happened. Both "agent" and "stressor" are used throughout Chapters 1-7 with no apparent distinction between them. The footnote implies that "agent" is the broader of the two terms, but that meaning is not apparent in the chapters. These terms should be clearly defined in the text and a glossary.
4	1/1-4	This sentence matches over 15 words from Barr, 2006; therefore, it should be in quotation marks.
16	4 (first in 2.3.4)/4	The sentence beginning with "The most critical…" should be revised. "The ability" object is singular but the subject of the sentence, "factors," is plural, making the sentence non-grammatical. Should this be "The most critical factor that influences… is the ability…"?
21	2nd bullet	Add "principles of exposure assessment"; this is a key component of the document cited.
27	3rd in 3.1.1/1-2	The passive construction of this sentence masks who should have this "necessary" and "thorough understanding." An active sentence construction with a clear subject would be more effective.
31	1st in 3.1.4/all	This paragraph is so close to the language in EPA 2015 (e.g., over 15 words are directly from this source) that it needs to be placed directly in quotations or completely rephrased to avoid the appearance of plagiarism.
32	Box 3-2/5th bullet	The link goes to the Source Water homepage. Keyword searching for "citizen involvement" did not turn up the source on August 7, 2016. This link needs to be updated.
33	last/last	"into" can be deleted and the line changed to "occupation), lifestages…" to make the grammar parallel.
39	1/6	A second paragraph could begin with "Incorporating…"
39	1/11	A third paragraph could begin with "The public…"

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
41	Box 4-2/8th bullet	The link provided in the References did not work on August 7, 2016.
42	Figure 4-1	This figure clearly shows where susceptibility fits in the schematic, but does not show where vulnerability is. The text at the bottom of p. 42 suggests that vulnerability incorporates the "receptor," "susceptible" and the two boxes at the bottom of the figure. Is that what the authors intend or is the entire box meant to represent "vulnerability?"
43	4.2 last paragraph/1-3	From "Considering," this repeats the first paragraph of 4.2.
43	4.3.1 1st paragraph/5-7	This important point needs a supporting citation; e.g., EPA 2005c.
44	first full/13	From "During" could be a new paragraph.
46	Figure 4-2/school line	Why aren't ages 3-5 indicated as "initiating activity?" Many children are in school-like settings during this "window."
47	4.3.4/9-12	It is not clear whether this statement is based on material in EPA 2005h or whether it is the author's recommendation. In fact, it may be based on both 2005c and 2005h. Please clarify.
50	5th bullet	Self-reported data are not necessarily reliable within any community. Language here implies that these data are problematic especially in tribal communities, when that is not the only case. This bullet should be revised.
51	last paragraph/1-2	This sentence needs to be more direct, indicating who should become "familiar."
57	last/13	The link here takes the reader to an administrative page with no apparent C-FERST content.
57	last/15-16	EPA's C-FERST says the tool prioritizes *issues*, not exposures. This sentence should be modified.
61	last/7	"potential future" sounds redundant. Wouldn't "potential" suffice?
63	2	The focus of this paragraph would stand out better with a subheading: 5.1.1. Available Data
63	4	A subheading (5.1.2. New Data) would help clearly distinguish this type of data from the discussion about existing data.
63	last bullet	Clarify uncertainty of what. The modeling outcome?
68	first bullet	When is "peer involvement" to occur? This bullet is not clear about the timing.
76	1/4-6	This quote is not in the resource cited. Identify the correct source.
76	last/1	EXPOsure toolBOX on August 7, 2016 was at https://www.epa.gov/expobox . This link needs to be updated in the document.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
77	5.3.4 1st paragraph/8-10	"needs to consider" seems too weak. Shouldn't this be a "must" statement?
77	5.4/4	"represent only some" begs the question as to how resources were chosen. If even one explicit criterion was used, then state it here.
78	2/6-8	Delete this sentence; it repeats the end of p. 77.
80	1/4	"only" should be deleted; existing data are discussed in the named sections (e.g., Table 5-3).
84	1st under the table/6-8	This sentence includes "need" and "needs." Modify to remove one of these "need/s." (same issue is in the second bullet on p. 85)
85	1st and 2nd bullets	Some sentences in these bullets repeat text at the bottom of p. 84.
86	1/3	Clarify what "published" means. The source content near this point indicates that published data and information were the basis. Some were not studies, but simply datasets. "Published data and information" would be more accurate than "studies."
88	Bullets 2-4	These should be sub-bullets to the first bullet.
89	1st under 5.4.6	This definition of "model" originates in NRC, 2007, which should be used as the citation here.
96	3rd row	The source listed led to "page not found" on August 6, 2016. The appropriate source and link should be located, so that the "3-year period" can be identified and explicitly stated here. As time goes by and technology continues to change, the years of the study may become important.
103	second in 6.1/7	"and" instead of "or" makes more sense to this reviewer.
105	first in 6.2.1/1	"selecting" would be a better word than "using" here.
108	Figure 6-1	This is quite similar to Figure 8-2, but with a different citation, neither of which could be readily retrieved with the links provided.
116	5/7	"Microenvironment" has already been defined twice before (pp. 37 and 82). This is an example of why a glossary for the whole document would reduce repetition and be a useful tool for the reader.
120	1-3/all	The Executive Summary and Introduction both say that this topic will not be included in the document. Therefore, these paragraphs should be deleted.
124	3/1	Although this definition for "sensitivity analysis" is the same as on p. 154, the source is later here than on that page. Usually the earlier citation is preferable.
124	3/1-3	Same issue as for "microenvironment" above.
130	7.2.5/13	The url is now different for the document, correctly named here.
133	7.2.10 2nd paragraph/10	The link here did not function on August 3, 2016. In fact, the October 2007 HSRB meeting documents are now archived by EPA.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
140	1/4-5	Delete the sentence in these two lines. It is redundant.
140	1/9-11	This sentence repeats other content in paragraphs 1 and 2.
140	2/10-12	These sentences are particularly puzzling. Are these referring to definitions and documents external to EPA? Is the last sentence referring to the documents in the prior sentence or to this draft?
142	Box 8-1	The definition for "sensitivity analysis" is found in EPA 2009c, earlier than either of the sources at the bottom of this box. Neither website could be retrieved on August 7, 2016. These need to be updated.
143	Table 8-1/6th row	Here is an example of an occupational group included in this draft. The staff paper (to which the citation [EPA 2004b] incorrectly links the reader) includes discussions about workers. The correct link should be to the Staff Paper (EPA/100/B-04/001) and not the Science Advisor's cover letter.
149	1/8	EPA 2001g could not be retrieved. Therefore, it is not clear whether 6.4 and Chapter 9 in the rest of this paragraph are referring to sections in these draft *Guidelines* or to parts of EPA 2001g. Clarification of this paragraph is needed.
157	1/2-4	Everyone has perceptions and biases which affect their interpretations. This sentence would be better including that reality, rather than limiting this concern to stakeholders, managers and decision makers.
158	1/11-12	Is this "Chapter 9" referring to the chapter in this draft or in one of the documents mentioned in this paragraph? Clarify to which source this statement is referring.
159	9.1	The title of this section is too broad for the content indicated by the title of the chapter.
168	9.5/5	The citation (EPA 2008a) links to the NERL program webpage and not to the SEAOES document; a better link is needed here.

P. Barry Ryan, Ph.D.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
3		This page is redundant with text
5	First paragraph	It should be stated that the endpoint for exposure may be different for different effects despite identical exposure
10	Table 2-2	Consideration of biomarkers of susceptibility and biomarkers of effect?
14	Table 2-3	What about exposures to multiple compounds with different toxicological endpoints?

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
16	Top	Discussion of analytical versus empirical distributions is warranted.
16	Second paragraph	Single-chemical versus aggregate- both are single chemical. Single pathway may differ from aggregate if multiple pathways are of interest.
19	Equation	Is a mono-layer assumed?
21	Fifth bullet	Are there examples?
30	Bottom bullets	Where do stakeholders figure in this?
34	First paragraph	Focus on first trimester and 1-18 months as these are the times most likely to affect outcomes for a lifetime
42	Figure 4-1	The Figure draws attention to those with the greatest potential risk, which is appropriate. However, other groups are at risk and not all with certain characteristics have equal risk. Can there be some expansion on this thought?
43	Top	Studies of fish consumption are very focused on one particular pathway of exposure at the expense of not as much information on other areas. This section would have the reader believe that fish consumption among subsistence anglers is an exposure pathway equivalent in importance to, for example, children's exposure to environmental compounds, in term of impact on the number of individuals. This is not the case. Subsistence anglers are a small, albeit important sub-group and perhaps even a sentinel sub-group, but they are not the only focus of USEPA's purview.
44	Last paragraph	Newborns, e.g., less than 1-3 months old, do not eat apples or even apple sauce.
45	Table 4-1	The age groups developed in USEPA 2005c are based on the thoughts of a panel of individuals and only very loosely based on any data collected (See USEPA 2005c) yet they are starting to be carved in stone.
46	Table 4-2	This is a useful Table, but I am uncertain as to the source of the information or on the validity of the data for various populations.
48	Table 4-2	The Potency Adjustments listed are almost completely arbitrary and are not based on. 10x is one log unit, 3x is a half a log unit, if log base 10 is used. One has no reason to assume that infants are 10 x more susceptible to exposures, as opposed to 100 x or 3x, than those over 16. These numbers are used frequently, and need some support.
48	2nd paragraph	The number 1,969,167 seems quite precise given the births and deaths of any population of this size during a one-year period.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
49	Box 4-4	There are either inconstancies or unclear parallels in wording in this Box
50	Last bullet	Are these based on anecdotal observations or evidence based?
56	Box 4-6	The version of the document I received had a missing term in "X=." Others commented on this in the context of completing the text
60	Third Paragraph	Is there a reference for the pesticide poisoning figure?
65	Bullet Points	Are these meant to be definitions?
67	Line 6ff	This is an important definition of DQOs
67	Third paragraph	Definition and description of QAPP Process
69	Fourth paragraph	It should be noted that reagents used in the analysis may, themselves, have background values. Acids, for example, often have trace metal concentrations in them. This must be accounted for in biological and environmental sample that measures very low levels of contaminants in various media. This is not "contamination" as suggested, as "contamination" has a pejorative sense to it, and is accounted for in blanks
70	First bullet	Should discuss effect of substitution on variance/standard deviation as well as mean. This is often forgotten.
71	Fourth Paragraph	The Dean methods are quite old and have been improved upon.
73	Figure 5-3	This Figure has been around for a while and I believe it has been "cleaned up" from this hand-drawn version.
75	Figure 5-4	This figure appeals to assume normality in the exposure estimate. Alternative strategies exist.
81	Table 5-3	This is a useful, albeit truncated, list of possibilities.
89	Section 5.4.6	Is this redundant with Chapter 6?
90	Section 5.5	Is this redundant with Chapter 8?
107	Section 6.2.2	I have some difficulty with this section as outline above in my main comments on the Chapter.
108	Figure 6-1	This Figure is simplistic, but does give a stepping-off point for discussion
108	First Paragraph	Sensitivity analysis can be performed using deterministic approaches through brute force variation of model inputs.
109	Figure 6-2	In the part of the figure illustrating probabilistic analysis, there is no indication (and no discussion in related text) of empirical approaches, i.e., random draw from a fixed dataset of observations. The discussion focuses on analytical

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
		distributions, e.g., normal, lognormal, uniform, exponential, etc. In addition, the curves on the right side of the Figure, for frequency and cumulative frequency do not represent the same process as the lower curve is the integral of the upper curve and should reflect the non-monotonic nature of the second derivative.
110	Third paragraph	There should be explicit definitions of Monte Carlo analysis and Latin Hypercube sampling stressing how they are related and the differences between them. Latin Hypercube may be more efficient, but makes some assumptions about the quality of the input data.
110	Last paragraph	There needs to be an expansion of what is meant by "… Some analyses might even involve simulations to evaluate temporal and spatial variability. …"
111	First Paragraph	Sensitivity can determine the importance of modeling parameters by affording a change in parameters by, say, x% resulting in a change in output by y% as an indicator. The term "one-dimensional Monte Carlo analysis" is not defined here or elsewhere. While there are references, it would be clearer if such terms, and distinguishing between one- and two-dimensional Monte Carlo approaches were indicated early on in the chapter as they are a focus of the discussion. For example, some 1-D analyses look only at variability while others include components of both that are not separated.
112	Third Bullet	Any type of quantification in Expert Judgment is problematic. One can look at agreement, but experts once agreed that the world was flat. How do we quantify expert judgement uncertainty? Experts almost always have estimates of such, but often such opinions are not correlated nor even relevant to reality.
114	Third Paragraph	Please define a "systems thinking approach." Do the authors mean holistic?
114	Fifth Paragraph	The Furtaw reference is 15 years old. Is it still relevant in this context? Even the Williams reference is six years old.
115	Second Paragraph	Is this not redundant with earlier sections?
115	CHAD	This database is now quite old. Is it time for an update?

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
116	Third Paragraph	Is not the Draft Protocol a bit dated? The pesticides used and their use patterns have changed substantially in the last 15 years.
118	First Paragraph	These are good examples.
120	Bullets	These require lots of data that may not be available for most compounds and inhuman subjects.
121	Third Paragraph	I think it is fair to question the utility of computationally complex models that cannot be validated.
124	Paragraph 1	How does one develop DQOs, a USEPA favorite requirement, if the model results cannot be validated? I see no way to accomplish this. Comparing with another model does not give any information if that model is equally unvalidated. Data may not be available to validate the model. Internal consistency- giving the same results for the same problems- is not "validation." A similar problem shows up on Page 123 Paragraph 5 in the discussion of uncertainty.
128	Paragraph 1	More generally, one should include IRBs at all locations, not just these.
129	Paragraph 4	Discussion of budget/sample size is key
129	Last Paragraph	I am not sure how these studies, out of the hundreds of sample size studies done, were selected for referencing.
131	Paragraph 4	Sample storage procedures are part of both protocol and CoC issues
133	Paragraph 3	It is not only EPA that has interest in these ethical issues, yet the text would suggest this is the case.
133	Paragraph 4	There was a great deal of work focusing on ethical issues done in the National Children's Study. This should be reviewed and included here.
133ff	Section 7.2.10	This entire section focuses on regulation rather than the "science" of ethical research. I think the focus should be on the latter.
134	Third Paragraph	It is not always either possible or feasible to collect personal samples of every type.
136	Section 7.2.13	Plan first- then design database.
137	Second Paragraph	Can use the main changes in the database design and implementation in the NCS as an example of what can happen
137	Third Paragraph	The TEAM Study is 30 years old.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
140	First Paragraph	The definition of decision uncertainty is weak and not particularly clear. More I needed.
141	Third Paragraph	Useful compilation of references for uncertainty in risk analysis.
142	Last Bullet	Expert Elicitation represents a different type of process from the other. The definition is odd. Why is it multidisciplinary? The definition does not suggest that. I am not sure that it should be in the "Box."
143	Table 8-1	Examples are an important part of this table. There should be one or more for each item to clarify the definitions. What are "population "figures" under Surrogate data? Discuss systematic versus random misclassification under that heading Random sampling error is generally quantifiable and has been in the purview of survey statisticians for 100 years. Under oversimplification- how does one address screening tools? Under Failure to Account for Correlations- How can one possibly know what is not known? Remember Rumsfeld's quote. The Description or Example under Model disaggregation is muddled and unclear.
144	First Bullet	It would be worth discussing here relationships between LOD and sensitivity.
145	Table 8-2	In row "Will using a combined dataset be a problem? The Question/Approach is not clear. What is "data of one type or another?"
145	Section 8.1.3	The whole section discussions variability, but does not address the impact of such on uncertainty. Have I missed something?
147-148	Bullets	Ultimately, the content of these bullets is focused on regulatory decision making. This document could address other frameworks as well.
149	Section 8.2.3	It would be helpful if some results were given here.
149	First bullet at bottom	Are input variables correlated? This can reduce the efficiency of collecting data, cf. temperature and ozone

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
151	Fifth Paragraph	Define the max and min for an analytic distribution that gives probabilities to infinity. For example, concentration of compounds in water, while following a particular distribution, cannot exceed the saturation concentration (solubility) before a phase change occurs. Sensitivity analysis- For an analytical definition of the exposure, could use the Bevington (1969) approach of expansion of variance in terms of partial derivatives: $$Var(Exp) = \sum_i \sigma_i^2 \left(\frac{\partial Exp}{\partial Xi}\right)^2$$ Where *i* indexes variables and factors
152	Figure 8-3	Are the colored data meant to represent "real" measured data? Is the model used normal or lognormal?
154	Fourth Paragraph	What about correlation among variables?
156	Role of Expert Elicitation	How does one quantify uncertainty? Are there some references to call upon here?
157	Section 8.4	Is this not the purview of Chapter 9?
159	Paragraph 4	This has been discussed in other Chapters
162	Box 9-1	I think this Box is misplaced here.
163	Paragraph 4	These are important examples (in Risk Characterization Handbook) but the Handbook is 16 years old.
164	Paragraph 2ff	This discussion appears self-contradictory. Presentation in numeric form is the best. Presentation in numeric form is not readily understandable and it loses the audience. Etc. Please clarify.
165-166	Media Discussion	This is quite interesting and perceptive. How do we get a better response from the media? Presentation of ideas would be good here, or stating that this would be an interesting area for research. There was much discussion by the panel on this topic.
166	Top	Public relations and press releases can be problematic.
167	Table 9-1	Referring to industry as non-credible sources and poor communication is pejorative and biased. Caution yes. Dismissals – no. Put in context. Some great data are available from industrial sources. As Penelope Fenner-Crisp pointed out, there would be no good data for pesticide regulation without industry data.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
		"Balance a negative statement with three positive statements." Where did this come from? What about water in Flint, Michigan? Name three positive things to say for every negative one about that. Was this meant to be proscriptive? If so, I cannot support the contention. Using humor is not necessarily poor communication or flippant. In fact, serious tone and no lightness can make presenters seem like "stuffed shirts" and "not like me." There are too many sweeping statements here.
168	Paragraph 4	The National Children's Study did a great deal of work on risk communication and ethics. This should be explored and referenced.

Alan H. Stern, Dr. P.H., DABT

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
11	Line 1	After, "chemical characteristics of the soil," add, "and the characteristics of the physical and chemical interactions of the specific metal and the specific soil."
17	Par. 4, line 1	"(discrete form)" here is not explained.
19	equation	While the attempt to generalize here is understood, it should also be acknowledged that this equation only applies under specific circumstances (e.g., low loading, non-allergenic endpoints).
49	Last bullet	Move "potentially" to after "are."
56	Box 4-6, first line after equation.	Something is missing (underscore).
111	Second par.	After, "…variables are selected randomly" add, "from input probabilistic distributions."
165	Par. 3, line 3	After, "…states and tribes" add, ", potentially responsible parties."

Clifford P. Weisel, Ph.D.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
37	Table 3.1	I do not agree with all of the examples presented. It is not clear how the examples for Exposure Pathway describe the movement of a contaminant from its sources to people. At best they are modifiers of movement. Site assessment is less a characterization of a population at risk than of a source.
62	Table 5.1	The term air should be separated into two boxes – ambient air and indoor air/vapor intrusion. The latter would just be for residents while the former for both populations. I am not sure why Naturally occurring food is listed for Biota.
82	Line 6	The direction of an aquifer's flow seems to be a strange example for the conditions data were collected on.
84	1st paragraph	On biomarkers to assess exposure: add 1) how differences in metabolism rate across individuals can affect the biomarker level to exposures 2) the need to know the time between exposure and the collection of sample 3) metabolism can vary with the route of exposure for rapidly metabolized compounds and 4) body mass can affect biomarker levels in different fluids for lipophilic compounds.
84	Table 5-4	Add Breast milk to media column.

Specific Observations for *Guidelines for Human Exposure Assessment*		
Page	**Paragraph**	**Comment or Question**
87	Table 5-5	For Activity frequency and tracking in the Collection method Use of GPS, For Examples: Not sure what Occupational tenure means. For Intake rates: Observational recording, Wearing Electronic Sensors
88	5th bullet	Page 88 – under What methods are available for conducting observation studies – did you mean GPS rather than GIS?
Starting 95	Table 5-6	It would be useful to provide years that that the data were collected in or the study was done and what media were being sampled. Add FDA for Food Basket Add ATSDR – Toxicological Profiles for individual compounds or groups of compounds. Page 100: US Census is out for 2010 Add TRI Data for Toxic Release Inventory Page 97 For RIOPA study – it was not an EPA study and the HEI Web site for accessing the data is https://riopa.aer.com/login.php
106	Table 6.1	The rationale used to organize this table is not apparent to me. For example an overview paper is in the middle
120	Top of page	Bullet points should also include issues of age, gender and polymorphisms
145	2nd paragraph	The definition of "inherent uncertainty" sounds more like variability. Is this the correct interpretation of inherent uncertainty in risk assessment?
142	Box 1	The explanation of Sensitivity analysis is convoluted.
143	Table 1-1	The example for Random Sampling Error is a poor choice and not very illustrative.

APPENDIX A: MEETING AGENDA

AGENDA

External Peer Review Meeting on EPA's *Guidelines for Human Exposure Assessment*

August 15, 2016 1PM to 5PM (EDT)
August 16, 2016 8:30AM to 5PM (EDT)

Day 1	Teleconference number (415) 655-0052	Code: 977-475-505
Day 2	Teleconference number (415) 655-0060	Code: 123-721-785

Day 1 Webinar Link: https://attendee.gotowebinar.com/register/6870508789306688770
Day 2 Webinar Link: https://attendee.gotowebinar.com/register/7658171431654734850

DAY 1 - August 15, 2016

12:30 PM	Meeting Registration & Sign-in
1:00 PM	**Welcome, Goals of Meeting, and Introductions** David Bottimore, Versar, Inc.
1:30 PM	**Introduction to the Meeting** Ed Ohanian, U.S. EPA
1:40 PM	**Overview of *Guidelines for Human Exposure Assessment*** Nicolle Tulve, U.S. EPA
2:00 PM	**Chair's Introduction and Review of Charge** Clifford Weisel, Chair
2:15 PM	**Observer Comment Session**
2:45 PM	*Break**
3:00 PM	**Discussion – Round Table General Overview Comments**
4:00 PM	**Discussion - Response to Charge Questions (Initial Question(s))**
4:50 PM	**Wrap Up**
5:00 PM	Adjourn

**Times for breaks and lunch are approximate and at the Chair's discretion.*

AGENDA

External Peer Review Meeting on EPA's *Guidelines for Human Exposure Assessment*

August 15, 2016 1PM to 5PM (EDT)
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Day 1	Teleconference number (415) 655-0052	Code: 977-475-505
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Day 2 Webinar Link: https://attendee.gotowebinar.com/register/7658171431654734850

DAY 2 - August 16, 2016

8:30 AM **Recap of Day 1 and Agenda for Day 2**
David Bottimore, Versar, Inc.

8:40 AM **Chair's Review of Charge for Day 2**
Clifford Weisel, Chair

8:50 AM **Observer Comment Session**

9:15 AM **Discussion – Response to Charge Questions (continued)**

10:00 AM *Break**

10:15 AM **Discussion – Response to Charge Questions (continued)**

12:00 PM *Lunch**

1:15 PM **Discussion – Response to Charge Questions (continued)**

3:00 PM *Break**

3:15 PM **Discussion – Response to Charge Questions (continued)**

4:30 PM **Wrap-up/Next Steps**
David Bottimore, Versar, Inc.

5:00 PM Adjourn

**Time for breaks and lunch are approximate and at the Chair's discretion.*

APPENDIX B: MEETING ATTENDEE LIST

External Peer Review Meeting for EPA's *Guidelines for Human Exposure Assessment*

Crystal City Marriott at Reagan National Airport
1999 Jefferson Davis Highway
Arlington, VA, 22202

August 15 and 16, 2016

LIST OF PEER REVIEWERS

Name	Affiliation
Paloma Beamer, Ph.D.	University of Arizona
Nicole Cardello Deziel, Ph.D., MHS	Yale School of Public Health
Penelope A. Fenner-Crisp, Ph.D., DABT	Independent Consultant
Christopher W. Greene, M.S	Minnesota Department of Health
Michael A. Jayjock, Ph.D., CIH	Independent Consultant
Rebecca T. Parkin, Ph.D., MPH	George Washington University
P. Barry Ryan, Ph.D.	Rollins School of Public Health of Emory University
Alan H. Stern, Dr.P.H., DABT	Independent Consultant
Clifford P. Weisel, Ph.D.	Environmental and Occupational Health Sciences Institute

External Peer Review Meeting on EPA's *Guidelines for Human Exposure Assessment*

Crystal City Marriott at Reagan National Airport
1999 Jefferson Davis Highway
Arlington, VA, 22202

August 15 and 16, 2016

LIST OF OBSERVERS (in-person)

Name	Affiliation
*Patrick Beatty	American Petroleum Institute
Nancy B. Beck	American Chemistry Council
Steven Bennett	Consumer Specialty Products Association
Charles Bevington	US EPA
Uni Blake	American Petroleum Institute
Michael Broder	US EPA
*Sarah H. Brozena	American Chemistry Council
*Pat Casano	General Electric Company
Matthew Crowley	US EPA
Michael P. Firestone	US EPA
Mary Greene	US EPA
Maria Hegstad	InsideEPA
Matthew Lloyd	US EPA
David Miller	US EPA
Edward V. Ohanian	US EPA
Nerija Orentas	US EPA
Hua Qian	ExxonMobil Biomedical Sciences, Inc.
Stephanie Sarraino	US EPA
Tom Sinks	US EPA
Nicolle Tulve	US EPA

*Provided oral public comments at the meeting

External Peer Review Meeting for EPA's *Guidelines for Human Exposure Assessment*

Crystal City Marriott at Reagan National Airport
1999 Jefferson Davis Highway
Arlington, VA, 22202

August 15 and 16, 2016

LIST OF OBSERVERS (via phone)

Name	Affiliation
*Scott Arnold	The Dow Chemical Company
John U. Bell	Halogenated Solvents Industry Alliance
Steven Bennett	Consumer Specialty Products Association
Charles Bevington	U.S. EPA
Virunya Bhat	NSF International
Melanie B. Biggs	U.S. Consumer Product Safety Commission
Uni Blake	American Petroleum Institute
Sarah H. Brozena	American Chemistry Council
Xinrong Chen	U.S. Consumer Product Safety Commission
*Emma Cheuse	Earthjustice
Stephen A. Covell	U.S. Forest Service
Michael P. Firestone	U.S. EPA
Julie W. Fitzpatrick	U.S. EPA
Lindsey Gnazzo	Counterpoint Strategies
Stephen Graham	U.S. EPA
Matthew B. Harney	Keller and Heckman, LLP
Maria Hegstad	InsideEPA
Jamie S. Heisig-Mitchell	Hampton Roads Sanitation District
Ann Johnson	U.S. EPA
Lindsey Jones	Texas Commission on Environmental Quality
Alan P. Kaufman	Toy Industry Association, Inc.
Mari Kent	International Association of Fire Fighters
Mike Koontz	Versar, Inc.
*Amy D. Kyle	University of California Berkeley
Marie Maks	Landis International, Inc.

Name	**Affiliation**
Michael Maynard	Honeywell International
Autumn Moore	Toy Industry Association, Inc.
Nathan Mottl	U.S. EPA
Eloise Mulford	U.S. EPA
Marian Olsen	U.S. EPA
Shaila Rao	Gowan Company
Miriam Rotkin-Ellman	Natural Resources Defense Council
Stephanie Sarraino	U.S. EPA
Cynthia Stahl	U.S. EPA
Jake Tyner	U.S. Chamber of Commerce
Linda M. Wilson	NYS Office of the Attorney General
Valerie Zartarian	U.S. EPA

*Provided oral public comments at the meeting