

# **Guidelines for Human Exposure Assessment Responses to Comments**

March 2018

## **Peer Review Meeting**

August 15–16, 2016  
Arlington, VA

and

## **Public Review**

January 7–March 22, 2016

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## Executive Summary

For several years, the U.S. Environmental Protection Agency (EPA or the Agency) has worked to incorporate advances in exposure assessment into an update of the 1992 *Guidelines for Exposure Assessment* that reflect the best science currently conducted across the Agency. EPA obtained broad participation in its efforts to revise the 1992 document. Outreach included a 2005 colloquium that assessed the state-of-the-science Agency practices and emerging issues; meetings with scientists and engineers from EPA, state agencies and the broader scientific community; and consultations with EPA's Science Advisory Board. The revised document, *Guidelines for Human Exposure Assessment* (Guidelines, Guidelines document), reflects these engagements and the many additional years of experience with exposure assessments. Following intra- and interagency reviews and clearance, the draft update to the Guidelines was released for public comment on January 7, 2016. The public comment period closed on March 22, 2016. Multiple consultations with the tribes were conducted during July 2016. The public and tribal comments were compiled and provided to the peer-review panel before the peer-review meeting. A peer-review meeting of the Guidelines document, convened by an independent contractor, was held on August 15–16, 2016. All comments (public, tribal and peer review) were compiled into one report and the Technical Panel reviewed and addressed them.

Table 1 and Table 2 summarize the submissions and comments, respectively. EPA received 23,565 submissions, 47 of which were sufficiently distinct to be classified as unique. These 47 submissions contained 988 comments. The peer-review panel provided 702 comments, the public (non-tribal) provided 273 comments, and tribal organizations (either a tribe or an organization designated by the tribes to represent their interests) provided 13 comments.

**Table 1. Total Number of Public and Tribal Submissions**

Submission Type	Count
Unique	47
Duplicate (Campaign)	23,518
Total	23,565

**Table 2. Total Number of Peer Review, Public and Tribal Comments from Unique Submissions**

Comment Type	Count
Peer Review	702
Public	273
Tribal	13
Total	988

Table 3 details the categories and subcategories of all comments received. When comments were relevant to more than one category or subcategory, expert judgement was used to determine the

most appropriate category/subcategory for categorization. When multiple comments were received on the same topic, each comment was counted individually.

**Table 3. Categories of Comments**

Category	Subcategory	Count <sup>a</sup>
Technical	Definitions	105
	Lifestages, Vulnerable Groups, and Populations of Concern	102
	Data	99
	Modeling	81
	Purpose and Scope	66
	Uncertainty and Variability	50
	Principles of Exposure Science/Exposure Assessment	48
	Planning and Scoping Problem Formulation	45
	Observational Studies	36
	Biomonitoring	25
	Aggregate and Cumulative Exposure Assessment	15
	Emerging Issues	12
	Peer Review	11
	Tiered Approaches	8
Editorial	Editorial	231
	Communication	51
	References	3
<b>Total</b>		<b>988</b>

<sup>a</sup>For comments that fall into more than one category/subcategory, expert judgement determined the most appropriate category/subcategory for categorization.

Every comment received was considered and addressed. Conflicting comments were considered collectively, ensuring consistency. The Technical Panel made the final decision on whether and how to revise the Guidelines document. When comments resulted in a change to the Guidelines document, the response states the text was revised. When a comment resulted in no revision, a rationale is provided (Table 4).

**Table 4. Summary of Responses to Comments**

Type	Count
Comments leading to revisions	557
Comments not leading to revisions	431
<b>Total</b>	<b>988</b>

Overall, commenters were supportive of the update to the Guidelines document and stated that EPA had done a credible job providing quality scientific content that is well written and organized. The peer-review panel found no significant technical or policy issues with the draft document. As is the case any time a panel of experts is asked to review materials,

recommendations on how to improve the document were made. The content below identifies the issues that the Technical Panel determined to be among the more significant comments received from the peer review panel and the tribes and public.

Several commenters stated the document contained redundancies. When applicable and appropriate, the Technical Panel revised the content to reduce redundancy and improve the flow of the text. For example, text in Chapter 3 related to data quality was moved to Chapter 5 and referenced in Chapter 3. Nevertheless, the Technical Panel decided that some redundancy is appropriate because users of the Guidelines document do not necessarily read the document in its entirety but rather focus on specific issues.

Several commenters recommended a glossary to ensure consistency in the definitions and use of terms. The Technical Panel chose to define terms upon their first use in the document and ensure consistent use thereafter throughout the document. This approach provides both a definition and context for each term.

Another point commenters raised was to include international materials and citations. Because EPA does not use the same practices and procedures as some international organizations, the Technical Panel chose not to include significant content from international entities. The Technical Panel, however, did cite documents that could be consulted to support the scientific content of the Guidelines.

Whether to include an emerging issues chapter/section has been a recurring theme associated with this document. Early in this document's development, the Technical Panel did include an emerging issues chapter, but the chapter was not well received during the intra- and interagency reviews. As a result, the decision was made to remove the chapter. Based on recommendations from the commenters, the Technical Panel added an emerging issues section at the end of Chapter 2, the content of which was developed on the basis of comments from the peer reviewers.

Some commenters recommended EPA adopt a more prescriptive approach in this Guidelines document for conducting exposure assessments. The approach the Technical Panel took emphasizes the importance of a rigorous planning and scoping and problem formulation process, while allowing individual programs to adopt the most appropriate exposure assessment methodology that meets their needs. This approach provides flexibility to accommodate differences across programs and allows programs to apply their experience when considering novel methods and approaches as exposure science and exposure assessment advance. As appropriate, content from the 1992 Guidelines has been included in this current Guidelines document.

A few commenters requested additional content on relevance of socioeconomic status and disparate exposures to chemical agents. The Technical Panel included an introduction to lifestages, vulnerable groups and populations of concern in exposure assessments in Chapter 4.

Tribal representatives provided updated information on the presentation of tribal issues and exposure assessment. The Technical Panel revised the tribal text to address these comments.

In summary, EPA received 988 comments from the public, tribal and peer reviewers. More than half the comments led to revisions to the document. Many comments addressed broken links. The majority of comments were editorial, which were intended to improve the presentation of the content rather than revise the technical content. None of the commenters raised significant technical or policy issues.

## **Curation and Organization of the Response to Comments**

The peer reviewers' and the public and tribal comments on the Peer Review Draft of the *Guidelines for Human Exposure Assessment* were coded initially by Submitter (name of reviewer); Topic (e.g., Communication, Definitions, Editorial, Purpose and Scope, References); and Comment Type (Peer Review, Tribal, Public). Comments were sorted into two categories: those that referred to text in a specific location of the document and those that referred to no specific part of the document or were generally applicable to the entire document. These two categories appear below as Other Comments, Location-Specific and Other Comments, Non-Location-Specific, respectively. A third category, termed Frequently Mentioned Comments, was identified after analyzing the comments. Frequently mentioned comments fell into one of four major themes: (1) Definitions of Terms; (2) Links, Hyperlinks, URLs; (3) Additional Case Studies, Examples, References; and (4) Tribal Concerns.

For each comment, the comment is presented below, verbatim, as the reviewer provided. EPA's response is presented directly following the comment. EPA provides a rationale for those comments for which the Agency did not revise the text.

## Frequently Mentioned Comments

### Definitions of Terms

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**Location: Chapter 1, Page 2, footnote**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Footnote in Chapter 1 was revised for clarity. Chapters 1 and 3–9 were edited to use the term “agent.” Chapter 2 was edited to use the term “stressor” for consistency with National Research Council documents.

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**Location: Chapter 2**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Definitions

**Comment Type:** Public

**Comment:**

1. Definitions: ACC suggests including the definitions as a glossary rather than as table (e.g. Table 2-1).
  - a. “Dose” – overall clarity and consistency is needed in definition. The definition could cause significant confusion regarding assignment of a default definition of “dose” to mean “internal dose.” ACC recommends defining “dose” as generally meaning the amount to which one (laboratory animal or human) is exposed, and explicitly state “internal dose” vs. “administered/applied dose” when meaning the amount absorbed into the systemic circulation.
  - i. Historical and current toxicological studies refer to the administered dose in animal studies as “dose” and if tools are used to measure or estimate an internal dose, it is explicitly stated as such. If the terminology for human exposure is changed such that “dose” now means “internal dose,” it will lead to inappropriate comparisons.
  - ii. It is also noted that the historical literature on human exposures also report exposure (dose) as the amount to which a human is exposed. Even in a pharmaceutical context, “dose” is the amount a person ingests, and not the



internal dose. As with the toxicology literature, an internal dose is referred to as such.

- iii. For dermal exposures, it is important to consider the absorbed dose, not only the concentration contacting the skin.
- iv. Finally, although “dose” is defined early as the internal dose, throughout the document the term “internal dose” is used quite often, highlighting the fact that this distinction is helpful to the reader.
- b. “Exposure point concentration” – this term is misleading as it could be interpreted as deterministic (as in the discussion on page 15 about point estimates under deterministic). ACC recommends use of “exposure point of interest concentration,” because the measurement point location could represent conditions including pristine or background as well as contaminated conditions.
- c. “Exposure Period” – In Table 2.1, it is not clear what “continuous contact” means, e.g. relative to drinking water.
- d. “Exposure Route” – In Table 2.1, the definition of “Exposure Route” discusses internal exposure (e.g., “The way an agent can enter a receptor”), but the definition for exposure in this table only includes external exposure. This is an inconsistency. Perhaps as indicated in the text the more appropriate term to use is “dose.”
- e. “Bioavailability” – Some define bioavailability as what is available after first pass metabolism. The current definition in Table 2.2 suggests that bioavailability is what is available before any metabolism (first pass or other) takes place.
- f. “Agents, Stressors and Chemicals”
  - i. While the Guidelines’ principal focus is on human exposure to chemicals, it also notes (in Chapter 1, page 2) that much of the discussion “can apply to exposure to biological and physical agents (e.g., noise, radiation, microbial hazards, nanomaterials) or other stressors.” Footnote 1 on page 2 of the document then explains that the term “agent” is used throughout the document to indicate “any entity that an exposure assessor might analyze.” But the footnote also explains that Chapter 2 is the exception to this statement because it incorporates the National Research Council documents where the term “stressor” is used. It is useful to understand why there are differences or inconsistencies in the document’s use of the terms “agents” and “stressors.” This inconsistency should at a minimum also be explained in Chapter 2 itself (and in Table 2-1) and the document should define both terms and explain how and why they are being used interchangeably.
  - ii. Since the document is largely focused on chemical exposures, the term “stressor” is not a neutral term. ACC recommends that EPA employ the term “agent” throughout the entire document, particularly as it is a neutral way of referring to the subject of the assessment. The term “stressor” when applied to mean “chemical” suggests that any chemical exposure, regardless

of the extent of the exposure, will exert a stress. This is not a valid assumption. It is only through a risk assessment, when exposure estimates are combined with hazard information can it be determined that a chemical is exerting a biological stress leading to an increased risk of an adverse outcome.

- g. “Peer Reviewer” – As discussed in depth in the general comments above, exposure assessment requires data and information from persons with expertise outside of those with exposure assessment expertise. Therefore, the definition of “peer reviewer” in the Guidelines should be expanded to better track EPA’s discussion of peer reviewers’ qualifications for “expertise” in EPA’s 2015 Peer Review Handbook.

**EPA Response:** Text not revised to include a glossary. Terms are defined upon first use in the document and then used consistently throughout. Definitions are consistent with EPA usage with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

Dose. Section 2.2.2 and Table 2-2 discuss and define dose terms. Section 2.2.2 includes the text “When considering dose terms, understanding that different disciplines use different terms to define the same concepts is essential. As an example, within exposure science, the term ‘exposure’ refers to the amount of agent in contact with an external exposure surface, whereas in toxicology, the terms ‘administered,’ ‘external’ or ‘potential’ dose refer to this metric. The definitions of the terms in Table 2-2 derive from their use in exposure science. This document uses the exposure science definition of ‘dose’—the amount of an agent that enters a receptor after crossing an exposure surface.” This text is consistent with the commenter’s request for clarity and consistency. Text not revised.

Exposure point concentration; exposure period; exposure route. The EPA usage of these terms is provided in Table 2-1.

Bioavailability. The EPA usage of this term is provided in Table 2-2.

The use of the terms “agent” and “stressor” has been clarified throughout the document, as described in Footnote 1 in Chapter 1.

Peer-Review is introduced in Section 3.1.4 with appropriate links to the 2015 Peer-Review Handbook for additional information. The Handbook includes examples and Worksheets to aid the users.

**Submitter:** American Petroleum Institute (API)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Definition of Dose. API is concerned that EPA will cause confusion in the way it has defined the term dose in Chapter 2. In the chapter, EPA implies that the term dose refers to an internal dose, i.e., the amount of agent that enters a receptor after crossing an exposure surface or absorption barrier, such as skin. This is inconsistent with the more general way dose used in the scientific literature. To

avoid confusion, EPA should define dose generally as the amount to which one is exposed and use the specific term “internal dose” to describe the amount that has crossed an exposure surface and reached an internal target. Throughout much of the Guidance, EPA does, in fact, use the term internal dose. The definitions in Chapter 2 should be revised to reflect this usage.

**EPA Response:** Text revised.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because terms are defined upon first use in the document. Definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007). “Stressor” is used in chapter 2 to reflect the role of exposure in the risk assessment framework. In subsequent chapters, the term “agent” is used.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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 have 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 as 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.

**EPA Response:** Text not revised because the text provides a thorough discussion of the terms “stressors” and “agents” with appropriate reference citations.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 2, Page 10, Table 2-2**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** Units for some of these concepts would help differentiate between dose and response.

**EPA Response:** Text not revised because Table 2-2 includes definitions and equations including units to calculate dose.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** Consideration of biomarkers of susceptibility and biomarkers of effect?

**EPA Response:** Text revised.

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**Location: Chapter 2, Page 12, 2nd bullet**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** Explain the difference between toxicity and potency.  
**EPA Response:** Text not revised because the focus of the document is on exposure and not toxicity.

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**Location: Chapter 2, Page 13, Section 2.3.2, point 1**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** “Exposure-response” is a new concept introduced here. This might require some explanation and contrast with dose-response.  
**EPA Response:** Text revised.

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**Location: Chapter 2, Page 19, equation**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** 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?  
**EPA Response:** Text not revised because “contact” is a general use term.

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**Location: Chapter 2, Page 7, 2nd paragraph, line 1**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

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**Location: Chapter 2, Page 9, Table**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because Table 2-2 provides descriptive definitions for key dose-related terms. Many different types of units would need to be included, resulting in confusion for the reader. Instead, we provide references for more information, including units.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text not revised because Table 2-1 defines this term as “Any biological entity (e.g., a human, human population, lifestage within a human population) that receives an exposure or dose.”

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**Location: Chapter 2, Pages 8-9, Section 2.2.1, 2nd paragraph, Table**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** Exposure period and exposure duration. I think something should be done to better explain the difference between these two concepts.

**EPA Response:** An example was added to the definitions for exposure period and exposure duration to show how these two terms are related.

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**Location: Chapter 2, Section 2.1**

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**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 5: “The endpoint for exposure science is the dose received by the target internal tissue or organ: the location where the dose initiates the toxicity pathways that trigger the adverse effect.”

This statement contradicts page 8, where the Guidelines note that “Exposure is the contact of an agent with an external boundary of a receptor.” Exposure assessment guidelines should have a consistent definition.

The language on page 5 includes ADME and as such may be considered an aspect of toxicology. However, exclusion of exposure measurements past the external boundary preclude[s] consideration of biomonitoring as exposure science tool. There are simple definitions of exposure science that would not result in contradictory statements (e.g., Exposure science is the study of human contact with chemical, physical, or biological agents occurring in their environments, and advances knowledge of the mechanisms and dynamics of events either causing or preventing adverse health outcomes [NRC 2012]).

**EPA Response:** Text revised.

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**Location: Chapter 2, Section 2.2.1**

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**Submitter:** Virginia Department of Environmental Quality (DEQ)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Table 2-2: Please clarify the difference between bioavailability and bioaccessibility.

**EPA Response:** Text not revised because bioaccessibility is not addressed in the document.

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**Location: Chapter 2, Section 2.2.2**

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**Submitter:** American Cleaning Institute (ACI)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** We have noted several instances where there are inconsistencies in language and definitions that could lead to misunderstandings or misinterpretation of the agency’s intent. Therefore, we believe further clarity should be provided for the following definitions and terms:

In Section 2.2.2, Dose Definitions (p. 8), we are concerned that there may be confusion in assigning the definition of “dose” to mean “internal dose.” We recommend leaving “dose” to generally mean the amount to which one (laboratory animal or human) is exposed, and explicitly indicate “internal dose” when describing the amount absorbed into the systemic circulation.

**EPA Response:** Text revised to ensure definitions of terms are consistent throughout document.

**Submitter:** American Cleaning Institute (ACI)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** In Table 2-1 (p. 9), within the definition of the term “Exposure Period,” it is not clear what “continuous contact” means. For example, what is the exposure period for something like drinking water (and its constituents) which is consumed regularly but the actual contact might be quite brief?

**EPA Response:** Text revised to include an example.

  

**Submitter:** American Cleaning Institute (ACI)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Further clarity should be provided regarding the terms “dose” and “exposure” in Section 2.2.2, Dose Definitions (p. 8).

**EPA Response:** Text not revised because the two terms are defined in Section 2.2.2.

  

**Submitter:** American Cleaning Institute (ACI)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** In Table 2.2 (p.10), with respect to the term “Bioavailability,” the definition suggests that it is what is available before any metabolism (1st pass or other) takes place. We note that there are other definitions of bioavailability that speak to what is available after first pass metabolism. Further clarification would be valuable.

**EPA Response:** Text not revised; no revision necessary because the definition includes concepts of both release from a medium and absorption by an organism.

  

**Submitter:** Consumer Specialty Products Association (CSPA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** CSPA requests additional clarity of the term “continuous contact” which is included within the Table 2.1 Definition of “Exposure Period”.

**EPA Response:** Text not revised because this is the definition of this term as published in the peer-reviewed literature (Zartarian et al., 2005).

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**Location: Chapter 2, Section 2.2.2**

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**Submitter:** CropLife America (CLA)

**Topic:** Uncertainty and Variability

**Comment Type:** Public



**Comment:** Pg 12: “The specific measures selected depend on the objectives of the exposure assessment and the availability of toxicity data.”

Oftentimes site assessments are designed to include chemicals for which toxicity data are limited or unavailable. This can be addressed in the uncertainty assessment part of a risk assessment.

**EPA Response:** Text not revised because specific recommendations for changes are not provided.

**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 10, Key dose-related terms, Table 2-2: “Biomarker (biological marker): An indicator of changes or events in biological systems. Biological markers of exposure refer to cellular, biochemical, analytical or molecular measures that are obtained from biological media such as tissues, cells or fluids and are indicative of exposure to an agent.” It is important to draw a distinction between biomarker of exposure and biomarker of effect.

Biomarkers of exposure include the parent chemical, metabolite, or interaction product at a target while biomarkers of effect are measureable biochemical or physiological alterations that are associated with a health outcome (WHO 2011). The scope of the Guidelines would focus the content on biomarkers of exposure.

**EPA Response:** Text revised to include a definition of biomarker of effect, consistent with Section 5.1.2.

**Submitter:** U.S. Department of Defense (DoD)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** This definition of delivered dose is no longer in Table 2-2, Key Dose-Related Terms, though the following is in the associated text: "The delivered dose is the amount of agent that is transported to the location where the adverse effect occurs." This is particularly important as later text states that the information in the table is what is used for an exposure assessment (page 12) "An exposure assessment can be used to develop any of the exposure or dose measures listed in Table 2-1 and Table 2-2."

Please add back this definition of dose used in the text to the table.

**EPA Response:** Text revised.

**Submitter:** U.S. Department of Defense (DoD)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** The term "exposure duration" was added to this table of definitions since the interagency review of the document. It would be useful to also add specific definitions of exposure durations.

Please add definitions for Chronic, sub-chronic, sub-acute, acute and also a term we are seeing more use of, short-term, to the table of exposure-related terms.

**EPA Response:** Table revised.

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**Location: Chapter 2, Section 2.3.2**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Page 13 (Section 2.3.2, #1) seems to use the term “intensity” to mean “magnitude,” but neither term is defined in Table 2-1. In that table, however, magnitude is used rather than intensity to define exposure assessment.

Clarification is needed.

**EPA Response:** Text revised.

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**Location: Chapter 3, Page 36, 2nd to last line**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** What is an “exposure area?”

**EPA Response:** Text not revised based on lack of specific recommendation. An “exposure area” is a specific location(s) where people might come into contact with a contaminated medium.

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**Location: Chapter 3, Pages 36-37, Section 3.3.1**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** What constitutes a “data gap?”

**EPA Response:** Text not revised because Chapter 5 provides information on defining and addressing data gaps.

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**Location: Chapter 3, Section 3.1**

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**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** \*\*Pg 26: “Better-informed decisions that use high-quality data, and are based on established objectives and use scientifically established methods”

A definition for “high quality” data should be included. Data quality is a critical aspect of interpretation of exposure and risk assessments and is also a key component of systematic reviews. At the same time, evaluations of data quality are often omitted or include only certain aspects of quality.

While there is a limited discussion of data quality later in the Guidelines, a comprehensive approach to evaluating data quality should be described in the Guidelines and also included here as part of the definition. One example of data quality assessment that pertains to biomarkers but could also be extended to environmental media can be found in LaKind et al. (2014).

**EPA Response:** Text not revised because Chapter 5 provides information on data quality and cites additional references. LaKind et al. 2014 provides a “proposal” for assessing data quality that is not accepted practice by the agency at this time.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Definitions for planning and scoping have been added to Section 3.1.

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**Location: Chapter 3, Section 3.1.1**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Additional content on communication, in particular “risk communication,” has been added to chapter.

---

**Location: Chapter 3, Section 3.1.3**

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**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 30: What constitutes “community”?

How/when do stakeholders and community overlap? Would an industrial stakeholder be precluded from participating in the development of an exposure assessment if they are not considered to be part of the “community”?

**EPA Response:** Text not revised; stakeholder, by definition (see Chapter 7), includes both the community and industry.

**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** \*Pg 31: “For routine or well-defined screening exposure assessments, input during planning and scoping might not be necessary, whereas for an exposure assessment that might be considered controversial, early stakeholder involvement is recommended”

A “routine” assessment should be defined so that all parties have a clear understanding as to when stakeholder involvement may occur. Consideration of a number of perspectives would better inform an exposure assessment- what is meant by routine and what is considered ‘controversial?’ Are there classes of exposure assessments one should consider when deciding how best to include stakeholder involvement?

**EPA Response:** Text not revised because an example of a routine assessment may be the comparison of the sample data from a well to the maximum Contaminant Level established under the Safe Drinking Water Act. An example of an assessment addressing a controversial issue may include the determination of a remedial action at a large abandoned hazardous waste site with exposures to multiple chemicals and pathways where the community is concerned about potential health effects from exposure.

Community involvement will vary depending on the legislative mandate regarding community involvement. The assessor needs to understand the context of the decision.

**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** p.30: In Box 3-1, “stakeholder” is defined, but “community” is not defined. I recommend providing a definition of community.

**EPA Response:** Text not revised because references are provided to appropriate guidance.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** The narrative on communication has been expanded throughout the document and revised to include more recent content. Although terminology might vary across the document (e.g., “engaging” and “involving” vs. “dialogue” and “communicating”), the intent is clear that these guidelines are advising the assessors to talk with the stakeholders from the outset of the planning through the decision and risk management process.

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**Location: Chapter 3, Section 3.1.4**

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**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 33, top: “Peer input” as distinct from peer review should be defined and distinguished clearly.

**EPA Response:** A definition of “peer input” has been added to the document.

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**Location: Chapter 3, Section 3.2.1**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to provide definitions of scenario and population-based approaches.

---

**Location: Chapter 4**

---

**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because Section 4.2 and Figure 4-1 include activities/behaviors in the description of vulnerability. Text from Section 4.2: “The population characteristics related to vulnerability (e.g., lifestyle, culture, diet, daily activities)...,” Figure 4-1, second bullet includes “activities.”

**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to define the terms vulnerability and susceptibility as used in the Agency. Text has been clarified to ensure that the terms are distinct and that

susceptibility is not a subterm of vulnerability. Text revised in both Section 2.1 and Section 4.2. References are included to support the text.

Exposure factors are found in the Exposure Factors Handbook and not this document. This document references the Exposure Factors Handbook.

Section 4.2 is not intended to set EPA policy, but to make the assessor and decision maker aware of elements that may need to be considered when conducting an exposure assessment.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** 1. Definitions:

- a. “Vulnerability” – A more balanced discussion of “vulnerability is needed. We recommend clarifying this discussion to acknowledge that different populations can be at both increased and decreased risk of adverse health effects.
  - i). In describing “vulnerable populations,” in some places EPA states “differential,” meaning it could be higher or lower, but in other cases the reference is only to higher risk.
  - ii). At the beginning of chapter 4, “vulnerability” is paired with “susceptibility” implying higher risk vs. differential risk. This is misleading.
  - iii). In section 4.2, it is stated clearly that “susceptibility” is a component of vulnerability referring to increased likelihood of impact/risk.
- b. “Differential susceptibility” is stated to lead to “increased susceptibility” which is not consistent with the meaning of the term as increased OR decreased. We recommend changing the definition to: “Differential susceptibility: an increased or decreased likelihood of sustaining an adverse effect from exposure to an agent.” The example provided should be revised accordingly.
- c. “Differential exposure” – EPA states that “[c]hildren have a higher exposure...,” but, for completeness, EPA should acknowledge that in other situations exposure can be lower or external exposure can be similar but internal dose can be lower (e.g., due to faster metabolism and excretion).

**EPA Response:** Vulnerability. Text revised.

Differential susceptibility and differential exposure. Text not revised because definitions are consistent with Agency use (U.S. EPA, 2003d).

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to clarify the definition of vulnerability in Section 2.1 and Section 4.2. In addition, Box 4-2 provides references for evaluating socioeconomic disparities in exposure, and Box 4-3 lists key sources of childhood exposure concentrations and exposure factors. Information is provided on the Community-Focused Exposure and Risk Screening Tool (C-FERST) and Tribal-FERST.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** “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.

**EPA Response:** Text revised in Section 2.1 and Section 4.2 to better define and distinguish the two terms vulnerability and susceptibility.

---

**Location: Chapter 4, Page 43, Section 4.3.1**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.)

**EPA Response:** Text not revised because the use of the term lifestage is consistent with EPA's approach.

---

**Location: Chapter 4, Page 47, Section 4.3.4**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** Fetal, childhood, etc. are called "age groups." Is there a reason these are not called lifestages? Is a distinction being drawn here?

**EPA Response:** Text not revised because age groups are part of the lifestage.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** End of first paragraph: fetal is part of childhood, according to the definition provided in 4.3.1, paragraph 1.

**EPA Response:** Text revised.

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**Location: Chapter 4, Page 54, last line**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** What is sensitivity in this context?

**EPA Response:** Text not revised because the text explains the index approach and the significance of the index results.

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**Location: Chapter 4, Page 58, 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** Is body burden defined anywhere? Are there other metrics as well? Body burden is not always a useful metric.

**EPA Response:** Text revised.

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**Location: Chapter 4, Pages 41-42**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.)

**EPA Response:** Text revised in Section 2.1 and Section 4.2 to better define and distinguish the two terms vulnerability and susceptibility.

---

**Location: Chapter 4, Section 4.2**

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**Submitter:** American Cleaning Institute (ACI)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** In Section 4.2 (p. 41), we note inconsistencies regarding the definition of “vulnerability.” The Guideline states that “vulnerability refers to characteristics of individuals or populations that place them at increased risk of an adverse health effect.” It is essential to acknowledge “vulnerability” can lead to higher or lower risk, rather than higher risk alone

**EPA Response:** Text revised to clarify the definition of vulnerability in Section 2.1 and Section 4.2.

---

**Location: Chapter 4, Section 4.3.2**

---

**Submitter:** American Cleaning Institute (ACI)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** In Section 4.3.2 (p. 44) regarding “vulnerability”, it is stated that “[c]hildren also have higher excretion and metabolic rates per unit of body than adults.” It should be noted that metabolic rates can actually be lower in young infants. Therefore, the statement be more comprehensive.

**EPA Response:** Text not revised because the paragraph discusses children and provides supporting references. The infant age ranges are not included in the discussion.

---

**Location: Chapter 5, Page 62, Table, last row**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** What is “naturally occurring food” as distinguished from locally grown food, fish, and game? Would this be things like wild berries and mushrooms?  
**EPA Response:** Table revised.

---

**Location: Chapter 5, Page 65, bullets**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** Are these meant to be definitions?  
**EPA Response:** Text not revised because the statement represents suggested activities to assess data needs.

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**Location: Chapter 5, Page 67, 3rd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** Definition and description of QAPP Process  
**EPA Response:** Text not revised because specific revisions are not identified.

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**Location: Chapter 5, Page 67, last paragraph**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** Can “secondary research” be defined? Is it the citation/application of an existing work?  
**EPA Response:** Text revised to include a link to a checklist and list of resources for evaluating secondary data from EPA’s National Exposure Research Laboratory (e.g., QAPP requirements for secondary research data).

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**Location: Chapter 5, Page 67, Line 6ff**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** This is an important definition of DQOs  
**EPA Response:** Text not revised because recommendations for changing the definition are not provided.

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**Location: Chapter 5, Page 70, Section 5.2.2., 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised to indicate that programs have specific definitions for quantification limits, MDLs, etc. For example, the procedure for quantifying the Clean Water Act MDL is described at <https://www.epa.gov/cwa-methods/method-detection-limit-frequent-questions>. Based on regulatory requirements, these definitions can vary and coordination with programs is recommended.

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**Location: Chapter 5, Page 73, Figure 5-3**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** It would be helpful to define the terms used in this figure.  
**EPA Response:** Text not revised because a reference is provided that includes the requested information.

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**Location: Chapter 5, Page 89, 1st paragraph under Section 5.4.6**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Definitions  
**Comment Type:** Peer Review

**Comment:** This definition of “model” originates in NRC, 2007, which should be used as the citation here.

**EPA Response:** Citation revised.

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**Location: Chapter 5, Section 5.2.1**

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**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 68: Repeat Question: What is the difference between peer involvement and peer input?

**EPA Response:** Text revised.

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**Location: Chapter 5, Section 5.2.2**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** 9. Page 71. Regarding Calculating Exposure Point Concentrations, ACC recommends using the term “exposure point of interest concentrations” to differentiate from a deterministic point assessment. We also suggest “point of interest” rather than “point of concern” as used elsewhere in the document.

**EPA Response:** Text not revised because the term “exposure point concentration” is defined and appropriate references are provided.

**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** p. 71: The term “modeling data” is introduced. Since model estimates reflect a conceptual model, a mathematical abstraction and simplifying assumptions, it seems prudent to differentiate measured data from model estimates.

Consider explicitly defining data in the guidelines, and using terminology that differentiates measurements from modeled estimates.

**EPA Response:** Text not revised because the term data is defined in the introductory paragraph to this chapter.

---

**Location: Chapter 5, Section 5.3.2**

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**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 73: “Biomarkers of exposure record the concentration of the chemical or its metabolites in biological media, whereas biomarkers of effect indicate cellular, biochemical or molecular change that occurs as a result of human exposure to the chemical (WHO 2004).”

This is a much better distinction between biomarker of exposure and effect compared to that given on page 10. The language should be consistent within the Guidelines.

**EPA Response:** Text revised to be consistent with definition in Box 2-2.

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**Location: Chapter 5, Section 5.3.3**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised since the terms reflect terms previously provided in the 1992 Guidelines.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** 16. Page 76, Box 5-2. “Reasonable” should be defined in context of Reasonable Maximum Exposure.

**EPA Response:** Text edited to emphasize this is a definition under the Comprehensive Environmental Response Compensation and Liability Act, the Superfund program. The definition was originally defined in the 1992 *Exposure Guidelines and Superfund Risk Assessment Guidance for Superfund Part A*, issued in 1989.

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**Location: Chapter 5, Section 5.4.5**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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?”

**EPA Response:** The terms “activity diaries” and “records” are comparable. Text bullets were restructured to improve clarity.

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**Location: Chapter 6, Page 110, 3rd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised since the definitions of the approaches and their relative advantages are well known. The purpose of this document is not to provide a full discussion of all issues relevant to the use of probabilistic models.

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**Location: Chapter 6, Page 114, 3rd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** Please define a “systems thinking approach.” Do the authors mean holistic?

**EPA Response:** Text revised and references added:

U.S. EPA. (2008d). White Paper: Integrated Modeling for Integrated Environmental Decision Making. (EPA/100/R-08/010). Washington, D.C.: U.S. EPA. [http://www.epa.gov/crem/library/IM4IEDM\\_White\\_Paper\\_Final\(EPA100R08010\).pdf](http://www.epa.gov/crem/library/IM4IEDM_White_Paper_Final(EPA100R08010).pdf)

NRC (National Research Council). 2012. Science for Environmental Protection: The Road Ahead. Washington, DC: National Academies Press.  
<https://www.nap.edu/catalog/13510/science-for-environmental-protection-the-road-ahead>.

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**Location: Chapter 6, Page 116, 5th paragraph, line 7**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review



**Comment:** “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.

**EPA Response:** Text not revised since terms are defined upon first use in the document. Definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

However, the term is used in multiple contexts and thus requires additional connotation at different places in the document.

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**Location: Chapter 6, Page 124, 3rd paragraph, lines 1-3**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** Same issue as for “microenvironment” above.

**EPA Response:** Text revised.

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**Location: Chapter 6, Section 6.3**

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**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 120-121: A number of terms need to be defined, including evaluation, validation and verification in this context.

**EPA Response:** Text revised.

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**Location: Chapter 6, Section 6.3.4**

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**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 124: “Prioritize sources of data uncertainty, decision uncertainty and variability”

Decision uncertainty needs to be defined and characterized here; while this term is defined in Chapter 8, that definition is not clear.

**EPA Response:** Text revised.

**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 124: "...such assessments usually are accomplished by performing univariate or multivariate Monte Carlo analyses, sensitivity analyses or contribution analyses or both."

"Contribution analyses" needs to be defined and characterized.

**EPA Response:** Text revised.

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**Location: Chapter 7**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 7, Page 129, Section 7.2.2**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** What is a "data element?" (also on previous page)

**EPA Response:** Text not revised because the first sentence in Section 7.2.2 defines a data element.

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**Location: Chapter 7, Section 7.2.3**

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**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** Pg 129: “The effect size is a measure of the differences between populations and is used to assess whether the differences are statistically significant.” This definition appears to be incorrect. “Effect size is a numerical way of expressing the strength or magnitude of a reported relationship, be it causal or not...”  
(<http://www83.homepage.villanova.edu/richard.jacobs/EDU%208603/lessons/statistical%20power.html>). For example, “A t-test’s effect size indicates whether or not the difference between two groups’ averages is large enough to have practical meaning, whether or not it is statistically significant”  
(<http://docs.statwing.com/examples-and-definitions/t-test/effect-size/>).

**EPA Response:** Text not revised because the definition is correct as used.

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**Location: Chapter 8**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text and definitions revised for clarity.

**Submitter:** CropLife America (CLA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** This chapter covers uncertainty and variability, topics that are essential to the development of a robust plan for conducting exposure assessments and for interpretation of data. The importance of this topic has grown since the focus of many risk assessments has shifted from persistent chemicals to those with short half-lives.

Despite this, Chapter 8 is difficult to understand; while definitions are given in Box 8-1, there is still undefined or poorly defined jargon (e.g., inherent uncertainty, decision uncertainty, interval estimate). The Guidelines are careful to distinguish uncertainty from variability in the definitions but then appear to conflate them in Section 8.1.3.

**EPA Response:** Text revised.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text and definitions revised.

---

**Location: Chapter 8, Page 140, 1st paragraph**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** The definition of decision uncertainty is weak and not particularly clear. More is needed.

**EPA Response:** Definition revised.

---

**Location: Chapter 8, Page 140, whole page**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** How do these definitions fit in with the uncertainty terms in Section 2.3.4?

**EPA Response:** Text not revised because specific recommendations were not provided. Text in Section 2.3.4 provides an overview of the concepts of uncertainty and links to Chapters 6 and 8 for more detailed discussion of uncertainty.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** How does parameter sensitivity fit into these definitions of uncertainty?

**EPA Response:** Text not revised; parameter uncertainty is defined in Box 8-1 and Table 8-1 and more generally in earlier sections of the Guidelines, for example, Sections 2.3.4, 2.7, 5.5 and 6.3.4.

---

**Location: Chapter 8, Page 141, Box 8-1**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** Bullet 1. Does uncertainty here refer to both data and decision uncertainty, as mentioned on page 140?

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 142, Box 8-1**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** Latin hypercube is not defined, while Monte Carlo analysis gets its own bullet after being mentioned in a previous bullet.

**EPA Response:** Text revised.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** The explanation of Sensitivity analysis is convoluted.

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 142, last bullet**

---

**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** 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.”  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 145, 2nd paragraph**

---

**Submitter:** Clifford P. Weisel, Ph.D.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** The definition of “inherent uncertainty” sounds more like variability. Is this the correct interpretation of inherent uncertainty in risk assessment?  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 145, Section 8.1.1**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Definitions  
**Comment Type:** Peer Review  
**Comment:** 2nd paragraph: “natural variability:” same as variability, as defined on page 140?  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Section 8.3**

---

**Submitter:** American Chemistry Council (ACC)  
**Topic:** Definitions  
**Comment Type:** Public  
**Comment:** 4. Pages 150-151, and Figure 8-2. The abbreviation 1-D MCA and 2-D MCA area used in the figure should be defined in the footnote to Figure 8-2 or clarified in the text.  
**EPA Response:** Text revised.

---

**Location: Chapter 9**

---

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

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

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

---

**Location: Chapter 9, Page 160, Section 9.2.1, last paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** “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?”

**EPA Response:** Text not revised since regulatory decisions lead to the establishment of standard or other actions. Determination of whether a standard has been exceeded is addressed in the evaluation of compliance.

---

**Location: Chapter 9, Page 161, 1st paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review



**Comment:** “Policy judgments:” different from “policy decisions” from previous pages?

**EPA Response:** Text revised.

---

**Location: Non-specific**

---

**Submitter:** American Chemistry Council (ACC)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** B. Definitions:

Several definitions in the Guidelines need clarification. Some of the more important terms that need attention include:

“dose” – internal dose or administered/applied dose. “dose” vs. “exposure”.

“vulnerability” – susceptibility vs. differential exposure. “exposure period” and the concept of “continuous contact”. “bioavailability”.

inconsistences[inconsistencies] in use of the terms “agents” and “stressors”.

the definition of “peer reviewer” in the context of exposure assessment. These definitions are discussed in detail below in Section III. ACC also recommends, however, (because the Guidelines’ General Exposure Related Terms in Table 2-1 is limited), that a glossary of important terms be added to the document. One suggestion for doing this is for EPA to pull out all the tables that serve as “mini-glossaries” throughout the document and condense these into a more comprehensive glossary of terms that also includes terms that don’t appear in any of the tables. Including a source or citation for every term in such a comprehensive glossary would also make it easier to update in the future.

**EPA Response:** Text not revised because terms are defined upon first use in the document and used consistently throughout the document. Definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

**Submitter:** American Cleaning Institute (ACI)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** There appear to be inconsistencies in the use of the terms “agents” and “stressors.” If they are synonymous, the definitions should indicate so.

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to include a summary of key points at the end of each chapter.  
Text not revised to include a glossary; terms are defined upon first use and definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; terms are defined upon first use in the document, and definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

**Submitter:** Consumer Specialty Products Association (CSPA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** CSPA raises concerns about the overall lack consistency with the definitions and language of ‘dose’ that results in a lack of clarity throughout the document. In particular, there is concern for significant confusion regarding the assignment of a default definition of “dose” to mean “internal dose”.  
  
CSPA recommends referring to “dose” as meaning the amount to which one (laboratory animal or human) is exposed, while explicitly state “internal dose” vs. “administered/applied dose” when meaning the amount absorbed into the systemic circulation. Historical and current toxicological studies refer to the administered dose in animal studies as “dose” and if tools are used to measure or estimate an internal dose, it is explicitly stated as such. If the terminology for human exposure is changed such that “dose” now means “internal dose”, it will likely lead to inappropriate comparisons between this document and much of the established research and literature. It is also noted that the historical literature on human exposures also report exposure (dose) as the amount to which a human is exposed. Finally, it should be noted that throughout the draft document, while “dose” is defined explicitly as the internal dose, the term “internal dose” is used repeatedly, highlighting the fact that this distinction is helpful to the reader. Consistent with this consideration is a request to the “internal dose” considerations into the definitions of “dose” and “exposure” in Section 2.2.1 and Section 2.2.2. It might

also be helpful to include a graphic similar to Figure 1-1 from EPA's Exposure Factors Handbook to minimize the likelihood of confusion  
([http://ofmpub.epa.gov/eims/eimscomm.getfile?p\\_download\\_id=522996](http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=522996))

**EPA Response:** Text not revised; terms are defined upon first use in the document, and definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

**Submitter:** Consumer Specialty Products Association (CSPA)

**Topic:** Definitions

**Comment Type:** Public

**Comment:** CSPA notes inconsistencies with the definition of "vulnerability" and recommends clarifying to ensure that the full vulnerability to a sub-population and all populations is properly communicated. It is essential to acknowledge "vulnerability" can lead to higher "vulnerability for specific sub-populations which inherently lowers vulnerability to other populations rather than exclusively higher alone. In the original Cumulative Risk Assessment guidance, "susceptibility" (or "sensitivity") is the exclusive term without the "differential" modifier. CSPA recommends aligning the current definition with the previous definition to improve clarity throughout the guidance.

**EPA Response:** Text not revised; terms are defined upon first use in the document, and definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; terms are defined upon first use in the document, and definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; terms are defined upon first use in the document, and definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

**Submitter:** National Tribal Toxics Council

**Topic:** Definitions

**Comment Type:** Tribal (Public)

**Comment:** Editorial issues: There are many inconsistencies in the text. Words like chemical, agent and stressor are used interchangeably but not necessarily meaning the same thing.

**EPA Response:** Text revised.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** The utility and clarity would be improved with the addition of a glossary.

**EPA Response:** Text not revised; terms are defined upon first use in the document, and definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Definitions

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

<b>Topic:</b>	Definitions
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	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.
<b>EPA Response:</b>	Text revised.
<b>Submitter:</b>	Rebecca T. Parkin, Ph.D., MPH
<b>Topic:</b>	Definitions
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	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.
<b>EPA Response:</b>	Text revised.

## Links, Hyperlinks, URLs

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### Location: Chapter 3, Page 24, 2nd paragraph, line 2

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<b>Submitter:</b>	Penelope A. Fenner-Crisp, Ph.D., DABT
<b>Topic:</b>	Editorial
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	Hyperlink in paper did not go straight to HHRA Framework. This one did: <a href="https://www.epa.gov/sites/production/files/2014-12/documents/hhra-framework-final-2014.pdf">https://www.epa.gov/sites/production/files/2014-12/documents/hhra-framework-final-2014.pdf</a> .
<b>EPA Response:</b>	Links updated.

---

### Location: Chapter 3, Page 31, Box 3-2

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<b>Submitter:</b>	Penelope A. Fenner-Crisp, Ph.D., DABT
<b>Topic:</b>	Editorial
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	Add hyperlink to the webpage for Public Involvement Policy and Related Documents.
<b>EPA Response:</b>	Link added.

---

**Location: Chapter 3, Page 32**

---

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Link not working properly

Public Participation Process for Registration Actions website. U.S. EPA.  
<http://www.epa.gov/pesticides/regulating/public-participation-process.html>

**EPA Response:** Link updated.

---

**Location: Chapter 3, Page 32, Box 3-2, 5th bullet**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Link updated.

---

**Location: Chapter 3, Section 3.1.3**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Links updated.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to update links and reference.

---

**Location: Chapter 4**

---

**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** 2. All the links in chapter 4 should be checked because many of them are not working correctly. For example, on page 40, the link to tribal science priorities has been directed to About the Office of Science Policy (OSP) webpage. The link to EPA-expo-box is not correct.

**EPA Response:** Links updated.

---

**Location: Chapter 4, Page 39, 1st paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Other hyperlinks in the document show the URL, but these do not.

**EPA Response:** Text not revised because hyperlinks and URLs are presented consistently throughout the document.

---

**Location: Chapter 4, Page 41**

---

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Link incorrect <http://www.epa.gov/risk/expobox/index.htm>.

**EPA Response:** Link updated.

---

**Location: Chapter 4, Page 41, Box 4-2**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The Expo-Box link redirects to the main page, epa.gov/risk. Change to <https://www.epa.gov/expobox>.

I didn't check the other links.

**EPA Response:** Link updated.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** --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

**EPA Response:** Text revised and hyperlinks updated.

---

**Location: Chapter 4, Page 41, Box 4-2, 8th bullet**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The link provided in the References did not work on August 7, 2016.

**EPA Response:** Link updated.

---

**Location: Chapter 4, Page 47**

---

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Link incorrect <http://www.epa.gov/swerrims/riskassessment/sghandbook/index.htm>

**EPA Response:** Link updated.

---

**Location: Chapter 4, Page 47, last line**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review



**Comment:** Hyperlink <http://www.epa.gov/swerrims/riskassessment/sghandbook/index.htm>). Doesn't get me there.

**EPA Response:** Link updated.

---

**Location: Chapter 4, Page 57, last paragraph, line 13**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The link here takes the reader to an administrative page with no apparent C-FERST content.

**EPA Response:** Link updated.

---

**Location: Chapter 4, Section 4.3.7**

---

**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** \*\*Pg 57, Geographic Location: Several of the links are not functioning.

The text in this section provides no guidance regarding how the information from the websites should be used to inform an exposure assessment. Further, the Guidelines do not give information on the quality of the data in the GIS- based maps.

Are these tools merely for background information so the exposure assessor can better understand neighborhood characteristics or are they meant to drive chemical selection and exposure inputs?

**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 63, 2nd Paragraph, line 4**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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](https://www.epa.gov/sites/production/files/2015-09/documents/consider_evaluate.pdf)

**EPA Response:** Text revised and URLs updated.

---

**Location: Chapter 5, Page 66, Box 5-1**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Links updated.

---

**Location: Chapter 5, Page 76, end**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** The Expo-Box link does not work. Remove the /risk from the URL.  
**EPA Response:** Link updated.

---

**Location: Chapter 5, Page 76, last paragraph, line 1**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** EXPOsure toolBOX on August 7, 2016 was at <https://www.epa.gov/expobox> .  
This link needs to be updated in the document.  
**EPA Response:** Link updated.

---

**Location: Chapter 5, Page 95, Table 5-6**

---

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 96, 3rd row**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Link updated.

---

**Location: Chapter 5, Section 5.3.3**

---

**Submitter:** CropLife America (CLA)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Pg 76: EXPOsure toolBOX link does not work.

**EPA Response:** Link updated.

---

**Location: Chapter 5, Section 5.4**

---

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Links updated.

---

**Location: Chapter 5, Section 5.4.4**

---

**Submitter:** CropLife America (CLA)

**Topic:** Data

**Comment Type:** Public

**Comment:** \*\*Pg 86, 5.4.4. Exposure Factor Information: EPA provides “key” sources for exposure factor information. Not all databases are equivalent in terms of strengths and weaknesses and the Guidelines would be greatly improved if cautionary information were given on this topic. (As an aside, the URL for the Consolidated Human Activity Database does not work.)

**EPA Response:** Link updated. Text not revised because text emphasizes planning, scoping and problem formulation as the basis for selecting factors. The chapter discusses

establishing data quality objectives before using existing data or collecting new data. What cautionary information is being recommended is not clear.

---

**Location: Chapter 5, Section 5.7**

---

**Submitter:** CropLife America (CLA)

**Topic:** Data

**Comment Type:** Public

**Comment:** Pg 95, Table 5-6: As above, some URLs do not work.

The larger issue is that no description is given regarding strengths and weaknesses associated with these various sources of data. If assessors are to weigh such strengths and weaknesses, they would need to know what they are within and between/among such sources of data.

**EPA Response:** URLs updated.

Text revised to emphasize coordination with the program. Descriptions of the data sets are provided so the reader can judge whether the reference might provide the types of data needed for a specific assessment.

---

**Location: Chapter 6, Page 106, last row**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The URL didn't work. Every URL in the document should be checked.

**EPA Response:** URLs revised.

---

**Location: Chapter 7, Page 130, Section 7.2.5, line 13**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The url is now different for the document, correctly named here.

**EPA Response:** Link updated.

---

**Location: Chapter 7, Page 130, Section 7.2.6**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** HEDS link is broken. This could be due to EPA doing a site redesign, temporarily(?) breaking some links.

**EPA Response:** Link updated.

---

**Location: Chapter 7, Page 133, Section 7.2.10, 2nd paragraph, line 10**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The link here did not function on August 3, 2016. In fact, the October 2007 HSRB meeting documents are now archived by EPA.

**EPA Response:** Link updated.

---

**Location: Chapter 8, Page 142, Box 8-1**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 143, Table 8-1, 6th row**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 151, Figure 8-1.**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** This is quite similar to Figure 8-2, but with a different citation, neither of which could be readily retrieved with the links provided.

**EPA Response:** Text revised to update Figure 8-2 to Figure 8-1. Reference to Figure 8-1 updated to EPA (2001h), RAGS Part III. The tiered approaches presented in Figure 8-1 relate to probabilistic analysis, while the approach in Figure 6-1 is specific to modeling. No revisions to figures are needed.

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**Location: Chapter 9**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Links updated.

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**Location: Chapter 9, page 168, Section 9.5, line 5**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The citation (EPA 2008a) links to the NERL program webpage and not to the SEAOS document; a better link is needed here.

**EPA Response:** Text revised.

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**Location: Non-specific**

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**Submitter:** American Cleaning Institute (ACI)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Finally, we would like to note that it was difficult to fully evaluate this document within the time permitted given the great number of underlying source documents that needed to be accessed, and the fact that a great number of the links to EPA websites were not functioning. All links referenced in the document need to be updated and access to key source documents should be provided in the docket for the Guidelines.

**EPA Response:** All links were updated.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text was revised and links updated.

**Submitter:** CropLife America (CLA)  
**Topic:** Non-substantive  
**Comment Type:** Public  
**Comment:** CLA has some very specific comments (Appendix document) regarding elements of the guidelines that are incomplete, lack detail or context, or are not readily understood. Links to documents, provided in the draft do not always function- we have highlighted that in some cases. We recognize the task before us, of reviewing and updating guidance that is over 20 years old- particularly given the changes in the scientific foundations as well as the tools used in the conduct of a risk assessment. For that reason, CLA will continue to review this draft and collect comments and concerns, and when the Peer Review Panel report is released for public comment, will plan to comment generally and specifically on that draft.  
  
We appreciate the opportunity to provide brief comments now, and also the opportunity to assess differences in this new guidance as compared with that of the historic documents used for human health exposure. Should you have any questions regarding this set of comments and questions, please feel free to contact me directly. We look forward to working with EPA as these guidelines are fully developed and tested for relevance and validity in assessing human exposure.  
**EPA Response:** Text revised and links updated.

**Submitter:** Generally agreed upon by all reviewers  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** It is important that all hyperlinks in the document work and that all models referenced are available on-line.  
**EPA Response:** Links updated.

**Submitter:** Michael A. Jayjock, Ph.D., CIH  
**Topic:** Editorial  
**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Links updated.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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](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](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/](http://www.epa.gov/risk_assessment/expobox/)

**EPA Response:** Links updated.



**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Links updated.

  

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Check all links

**EPA Response:** Links updated.

  

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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/>)

**EPA Response:** Links updated.

  

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** References and links updated.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** For some terms (such as sensitivity analysis) linked documents either did not include the quote or could not be retrieved using the links provided.  
**EPA Response:** Links updated.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** The document is largely accurate, although, some sections would benefit from additional information and updated hyperlinks.  
**EPA Response:** Text revised and links updated.

## Additional Case Studies, Examples, References

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### Location: Chapter 2

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** 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.

**EPA Response:** Text not revised because the document cites the *Draft Protocol for Measuring Children’s Non-Occupational Exposure to Pesticides by All Relevant Pathways* (U.S. EPA 2001b). This reference includes equations for estimating exposure via the inhalation and dermal routes of exposure.

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**Location: Chapter 2, Page 15, after bullets**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because providing examples for all scenarios, methods, practices, etc., would significantly increase the length of the document.

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**Location: Chapter 2, Page 21, 5th bullet**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** Are there examples?  
**EPA Response:** Text not revised because the text provides references to the NHANES webpage that includes a web-based tutorial and references to study analyses.

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**Location: Chapter 2, Section 2.3.3**

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**Submitter:** American Chemistry Council  
**Topic:** Uncertainty and Variability  
**Comment Type:** Public  
**Comment:** Page 16, EPA states: “Probabilistic approaches can be used to better depict the uncertainty and variability in influential input variables.” Beyond the few publication examples cited by the Agency, we recommend that EPA compile a comprehensive listing of all EPA exposure and risk assessments that relied on probabilistic treatment of exposure inputs. A listing of all examples across Agency headquarters and regional offices, in addition to those cited in this document, where EPA has accepted PRA (e.g., from third parties) would be a valuable addition to this guidance document.  
**EPA Response:** Text not revised because the references include the document *Risk Assessment Forum White Paper Probabilistic Risk Assessment Methods and Case Studies*, published by EPA in 2014.

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**Location: Chapter 3**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Planning and Scoping and Problem Formulation  
**Comment Type:** Peer Review  
**Comment:** “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.

**EPA Response:** Text revised.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** In Section 3.2.1 Individuals/Lifestyles/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](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/sites/production/files/2015-05/documents/problem\\_formulations\\_for\\_human\\_health\\_risk\\_assessments\\_of\\_pathogens\\_in\\_land\\_applied\\_biosolids.pdf](https://www.epa.gov/sites/production/files/2015-05/documents/problem_formulations_for_human_health_risk_assessments_of_pathogens_in_land_applied_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.

**EPA Response:** Text revised.

The order in which assessments are developed (exposure or hazard identification) varies depending on the purpose of the assessment; in some cases, a sequential process is used, while in others, a parallel approach is used. The order can be determined during planning and scoping and problem formulation to fit the purpose of the assessment.

The Executive Summary and Section 1.2 explain that occupational exposures are beyond the scope of the document.

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**Location: Chapter 3, Page 27, Section 3.1.1, 2nd paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** This paragraph could use some concrete examples: What does this sort of thing look like in real life?

**EPA Response:** Text not revised because guidance is provided and presentation of specific plans is beyond the scope of this document.

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**Location: Chapter 3, Page 28, 3rd paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** Can the text provide examples of each type of assessment (Screening, lower tier, complex)?

**EPA Response:** Text not revised because EPA programs conduct a wide range of assessments in each of the categories and providing examples for every type of assessment would greatly lengthen the document.

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**Location: Chapter 3, Page 34, end of page**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** This whole section (3.2.2) is good, but would benefit from some concrete examples. Maybe link to some existing conceptual model descriptions.

**EPA Response:** Text revised.

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**Location: Chapter 3, Page 35, 2nd paragraph after bullets**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the text emphasizes the importance of coordination with appropriate programs for specific guidance.

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**Location: Chapter 3, Section 3.2.1**

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**Submitter:** CropLife America (CLA)



**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Public

**Comment:** Pg 33: “Scenario-based approaches commonly are used for several purposes...”  
Examples of “purposes” for which scenario-based approaches are used should be included in the guidance.

**EPA Response:** Text revised.

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**Location: Chapter 3, Section 3.3**

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**Submitter:** CropLife America (CLA)

**Topic:** Data

**Comment Type:** Public

**Comment:** \*\*Pg 36: “Resources for technical study design for different types of data acquisition approaches are presented in Box 3-3.”

Data acquisition is the foundation of a robust exposure assessment. The lack of detailed information here is surprising; more comprehensive citations are needed for Box 3-3 (the only two EPA references shown are for cancer risk assessment - which contains only a few pages on exposure assessment - and fish and wildlife consumption information).

Numerous books and guidance documents on exposure assessment have been published by top researchers in the field and these would likely offer the reader up-to-date and better overviews of study design considerations (e.g., Nieuwenhuijsen 2015; and OECD 2013). In addition, important aspects of study design that impact overall data quality have been described (LaKind et al. 2014).

**EPA Response:** Text not revised because subsequent chapters provide information on data (5), modeling (6) and planning an observational human exposure measurement study (7).

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**Location: Chapter 3, Section 3.4**

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**Submitter:** CropLife America (CLA)

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Public

**Comment:** \*\*Pg 38: “An exposure assessment plan need not be a lengthy or formal document, especially for assessments that are routine or well established” It is not clear what is meant by not needing a “formal” plan. Exposure studies are complex and the reliability of the study outcome (exposure or risk assessment) is related to the quality of the data both in terms of the extent and type of data and also the quality of all aspects of data acquisition.

This kind of statement downplays the importance and complexity of the exposure assessment. At the very least, specific examples of “routine or well established” assessment should be provided.

**EPA Response:** Text revised.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because appropriate references are provided with examples of communication procedures in selected programs, for example, Superfund.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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#### **Location: Chapter 4**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:**

Chapter 4 addresses the issue of environmental justice -- a legitimate concern that can be addressed directly in the exposure assessment as long as data can establish there are in fact greater exposure circumstances for a unique cultural and/or racial group. The chapter takes a broad brush approach to the issue, however, that could be misinterpreted and applied inappropriately by exposure assessors.

For example, in Chapter 4, EPA equates increased exposure with increased sensitivity under the umbrella of environmental justice, although the two risk assessment parameters cannot be assumed to be causally linked. Increased exposure potential does not necessarily equate to increased susceptibility, a fact that EPA should recognize in the Guidelines. Moreover, concern about greater sensitivity for a specific cultural and/or racial group is primarily a hazard-related issue rather than an exposure issue; therefore, it is better addressed in the risk assessment and risk management phases of the risk characterization.

If there is evidence that cultural and economic issues affect exposure in specific assessments, this should be reflected in the exposure data and factored in the specific risk assessment accordingly. Direct evidence of increased exposure based on cultural and economic issues would also prompt consideration of whether there are also biological parameters that indicate a unique sensitivity issue. If there is confidence in the scientific validity of the relationship between increased exposure and increased susceptibility, based on specific scientific evidence, this can be addressed through adjustments (e.g., uncertainty factors) in the risk assessment. Obviously, when such concerns are to be addressed, transparency in the risk characterization is very important, i.e., EPA must explain the scientific basis for its conclusion that there is a potential impact from exposures on more sensitive populations.

Rather than conflating sensitive subpopulations with populations subject to greater exposure potential, Chapter 4 should focus its guidance on lifestages and sensitive populations to those aspects that are important to the science of exposure assessment, e.g., describing evidence for greater exposure among certain populations. Chapter 4 should discuss whether, and if so how, the Agency is planning to use "disproportionate exposure" to go beyond the currently accepted uses of uncertainty factors. Chapter 4 should eliminate those sections (especially pages 53 through 57) that broadly equate increased exposure equivalence with increased sensitivity. Certain socio-economic and racial factors may produce unique exposures, but as suggested above these can be addressed in the risk assessment and risk management stages, rather than in the exposure assessment. Exposure demographics should not underlie the guidance or drive decision-making based on precautionary assumptions. Rather, EPA assessments should be derived using objective, transparent, and interpretable data.

Finally, Chapter 4 illustrates the general lack of examples in the Guidelines. Throughout the draft there are numerous references to other documents for the assessor to find additional details on some of the technical approaches and topics to consider when planning and conducting an exposure assessment, but no references to examples where the approaches have been used. Section 4.4 addresses

identification of life stages, vulnerable groups and populations of concern for exposure assessment, but fails to include references to examples.

ACC recommends that EPA modify Chapter 4 to ensure its focus is appropriately on the science of exposure assessment. This chapter – and indeed the entire document -- would benefit greatly from the addition of more examples.

**EPA Response:** Text revised.

**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Chapter 4: This chapter discusses the consideration of vulnerable groups. This chapter lacks text discussing how risk assessors and risk managers work together to address vulnerable groups. In place of text describing these interactions, the guidance provides examples that confound risk assessment, risk management and societal judgment. This chapter should focus on how the exposure scientist works with the risk manager to ensure that vulnerable groups are included in the assessment, and refer the reader to relevant resources on risk management.

For example, the text on page 54 regarding income inequality goes beyond the scope of exposure science. The Atkinson index in Box 4-6 requires a risk management assumption weighting the “degree of aversion to disparity,” and requires an estimate of individual risk, both of which are beyond the scope of exposure science. In Box 4-6, it is stated that the “multipollutant approach reduced AI by 2.241% compared to baseline,” but it is unclear what relevance this has to exposure science, or whether this finding translates to meaningful reduced hospitalizations in the vulnerable group of concern. Metrics such as the Atkinson index obscure actual physical quantities such as personal exposure concentrations of individuals in a vulnerable and control group, and require judgments that are not within the scope of an exposure scientist.

The use of detailed specific examples in Chapter 4 is inconsistent with the remainder of the document where specific examples are not used. For example, on page 21, the existence of approaches developed under the European REACH is mentioned, but the guidance does not describe in detail specific models or approaches that have been developed as part of chemical registrations. Therefore, it is recommended that this chapter eliminate the focus on specific examples such as the Gini index or Atkinson index, and instead focus on identifying the groups to be considered, and the nature of the information exchange between exposure scientists, risk assessors and social scientists that occurs when addressing vulnerable populations. For example, what types of exposure information would be required to conduct an income inequality assessment, and how is this the same or different than general population assessments? The text should also address how exposure scientists can improve transparency in vulnerable group assessments by including absolute measure of exposure (e.g. personal exposure concentrations by group) when indices are applied.

**EPA Response:** Text not revised because the initial paragraphs include information the exposure assessor needs to consider regarding vulnerable groups and coordination between the exposure assessor and risk manager/decision maker. A link to Section 3.2.1 is included, which discusses this relationship in more detail.

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**Location: Chapter 4, Page 43, Section 4.3.1, 1st paragraph, lines 5-7**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** This important point needs a supporting citation, e.g., EPA 2005c.  
**EPA Response:** Text revised.

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**Location: Chapter 4, Page 47, Section 4.3.3, 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** Thank you for including examples here.  
**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter.

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**Location: Chapter 4, Pages 42-43, 2nd bullet**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** I appreciated the inclusion of some real-world examples here. If possible, this should be done a lot more in the document.  
**EPA Response:** Text not revised because EPA included examples, where appropriate.

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**Location: Chapter 4, Section 4.3.3**

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**Submitter:** CropLife America (CLA)  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Public  
**Comment:** Pg 47: "Exposures to indoor air pollutants from spending time indoors might be greater at the extremes of age: the very young and very old."

A reference supporting this statement is needed. For example, people in middle age may spend most of their time at an indoor job and then at home. It is important that these kinds of observations be supported with data.

**EPA Response:** Text not revised because the first paragraph of Section 4.3.1 indicates the importance of understanding activity levels and how these levels vary with lifestyle.

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**Location: Chapter 4, Section 4.3.7**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** 10. Page 56 Box 4-6, “Applying the Atkinson Index.” If the discussion of income inequality and various indices of same are retained in these Guidelines, the example of the Atkinson Index requires clarification. Details on aspects of the analysis are lacking. What value was used for  $\epsilon$ ? What was the value based upon? What does variable X in the AI equation represent? Is 2.2% significantly different? Do the results for mortality risk, which differ only by 0.0007 for multi-pollutant as compared to status quo analysis, support the statement that “for both asthma and mortality, the multi-pollutant approach does a better job than the status quo”? Why is an example included for this particular concept in the document, when few examples of other central concepts are demonstrated?

**EPA Response:** Text not revised because Box 4-6 provides a citation for additional information.

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**Location: Chapter 4, Section 4.4.2**

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**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Pg 58: “Although case studies might lack statistical power, they can be valuable for describing past exposures or understanding how and why certain exposures happened. They are particularly important when documentation of past exposures is lacking or when a particular exposure was proposed but ultimately did not happen.”

It is not clear what is to be gained from a case study for a location where an exposure was

“...proposed but ultimately did not happen.”

**EPA Response:** Text revised.

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**Location: Chapter 5**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** The document's discussion of biomonitoring in Chapter 5 could be significantly improved. Section 5.3.2 discusses the limitations of biomonitoring data, but the Guidelines fail to reference the Centers for Disease Control and Prevention's (CDC) discussion of interpreting the biomonitoring information it collects through NHANES:

The measurement of an environmental chemical in a person's blood or urine does not by itself mean that the chemical causes disease. Advances in analytical methods allow us to measure low levels of environmental chemicals in people, but separate studies of varying exposure levels and health effects are needed to determine whether such blood or urine levels result in disease. (Fourth National Report on Human Exposure to Environmental Chemicals 2009 (page 8) <http://www.cdc.gov/exposurereport/pdf/fourthreport.pdf>. Given the CDC's expertise in biomonitoring, this is a significant oversight. The Guidelines should reference this important CDC caveat regarding biomonitoring data.

In addition, the Guidelines indicate that the utility of "biomonitoring equivalents" data is limited to characterizing human exposures. EPA effectively ignores the application of biomonitoring data in risk assessment when it states: "...the data on biologically equivalent doses that result in toxic effects are limited, making the comparisons necessary to assess health risks difficult." This is an outdated viewpoint.

Biomonitoring equivalents (BEs) published in the peer-reviewed literature are available for roughly 90 compounds and elements, and this number continues to grow.<sup>22</sup> Moreover, risk-based internal dose metrics are available for a number of additional analytes from other sources, such as Health Canada,<sup>23</sup> the German Human Biomonitoring Commission,<sup>24</sup> and EPA ORD scientists.<sup>25</sup> Certainly, the quality and reliability of available BEs should always be examined on a case-by-case basis, and used if determined to be of good quality and reliable. The Guidelines accurately point to the limitations of biomonitoring data that must be considered, noting "[b]efore relying on biomonitoring data for an exposure assessment, the project team needs to be cognizant of limitations inherent to the biomarkers used." (page 74). ACC concurs with this position, and bring EPA's attention to a publication of a similar treatment available in the literature.<sup>26</sup> The Guidelines should include a more current discussion of the application of biomonitoring data in risk assessment.

There are several other questionable statements in the discussion of biomonitoring and biomarkers in the Guidelines relating to biomarkers following a single exposure; not accounting for chemicals that are produced endogenously in the body or from metabolism; links between exposure and health effects; failure to adequately account for ADME and PK concepts; biological variability; and the



overall quality of biomonitoring data. These issues are discussed below in the Detailed Comments section covering both Chapters 5 & 6. ACC recommends that EPA update its discussion of biomonitoring as discussed above.

Footnotes:

- <sup>22</sup> Aylward LL, Kirman CR, Schoeny R, Portier CJ, Hays SM. 2013. Evaluation of Biomonitoring Data from the CDC National Exposure Report in a Risk Assessment Context: Perspectives across Chemicals. *Environmental Health Perspectives* 121 (3): 287-294.
- <sup>23</sup> St-Amand A, Werry K, Aylward LL, Hays SM, Nong A. Screening of population level biomonitoring data from the Canadian Health Measures Survey in a risk-based context. *Toxicol Lett.* 2014 Dec 1;231(2):126-34. doi: 10.1016/j.toxlet.2014.10.019. Epub 2014 Oct 17.
- <sup>24</sup> Angerer J, Aylward LL, Hays SM, Heinzow B, Wilhelm M. 2011. Human Biomonitoring Assessment Values: Approaches and Data Requirements. *Int J Hyg Environ Health* 214(5):348–360.
- <sup>25</sup> Phillips MB et al. 2014. A new method for generating distributions of biomonitoring equivalents to support exposure assessment and prioritization. *Regulatory Toxicology and Pharmacology* 69: 434-442.
- <sup>26</sup> Stahl Jr. RG, Bingman TS, Guiseppi-Elie A, Hoke RA. 2010. What Biomonitoring Can and Cannot Tell Us about Causality in Human Health and Ecological Risk Assessments. *Human and Ecological Risk Assessment: An International Journal* 16(1): 74- 86.

**EPA Response:** Text revised.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Link updated. Text revised to include additional references for evaluating non-detects.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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 ongoing 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.

**EPA Response:** Text and Table 5-6 revised.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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: <http://pubs.healtheffects.org>).

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](https://www.cdc.gov/nchs/data/nhanes/nhanes_release_policy.pdf))

**EPA Response:** Text added in Section 5.4 regarding the new federal policy on making raw data available for research conducted with federal funding. Providing an overall policy on access of raw data not associated with this policy is beyond the scope of the Guidelines for many of the reasons provided in the comment.

Text revised to include the following resources: Checklist and list of resources for evaluating secondary data and EPA's National Exposure Research Laboratory QAPP requirements for secondary research data. These documents provide considerations when combining multiple datasets, particularly those of differing quality.

The reference to OPP (2000), *Assigning Values to Non-detected/Non-quantified Pesticide Residues in Human Health Food Exposure Assessments*, available at <https://archive.epa.gov/pesticides/trac/web/pdf/trac3b012.pdf>, was added to the document as another resource for evaluating non-detect values.

Discussion of the DQO process and the forthcoming systematic review policies and practices is beyond the scope of this document.

The figure depicting a conceptual model introduced in Chapter 3, Section 3.2.2 was referenced in this section.

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**Location: Chapter 5, Page 67, middle of 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** "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.)

**EPA Response:** Text revised.

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**Location: Chapter 5, Section 5.2.2**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** 5. Page 70 section 5.2.2. Only one literature reference and one model link are provided for this section. Limited practical information on how to address non-detects is included. The document should cite the useful 1992 Guidelines discussion in section 5.1.2.2.1 Evaluation of censored data sets, which describes in more detail the strengths and limitations of available approaches.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** Page 71. Regarding Combining Data Sets and Modeling Data, reference to meta-analysis principles and techniques would be useful inclusions.

**EPA Response:** Text not revised because this topic is beyond the scope of the document.

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**Location: Chapter 5, Sections 5.2 and 5.3**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** Chapter 5. The discussion of Data for Exposure Assessment would benefit from additional references and/or examples in the last paragraph on page 69, last paragraph; the sections on combining datasets and modeling data and bounding estimates on page 71; and the first paragraph on establishing baselines or reference levels on page 74.

**EPA Response:** Text not revised because providing examples for all scenarios, methods, practices, etc., would significantly increase the length of the document.

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**Location: Chapter 6**

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**Submitter:** American Cleaning Institute (ACI)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** In recent years, EPA OCSPP has appeared to emphasize consumer exposures in its various programs. Chapter 6 (Computational Modeling for Exposure Assessment)

should have greater emphasis and more information regarding deterministic human exposure models especially with respect to consumer exposures to chemicals in products which are often quite low. There is mention of EPA Exposure Assessment Tools and Models in the Guidelines.

However, there is a great body of work in the scientific literature that is not mentioned. The EPA Exposure Assessment Tools and Models alone are not sufficient and in some cases have not kept up with emerging science and relevant case studies. While it is not reasonable to expect that the Guidelines could fully represent the entire scientific database that is available in this area, there should be reasonable coverage of the available science. To the extent the Guidelines are intended for EPA program office staff, they should be encouraged to seek out and use all information sources relevant to the exposure (and risk) assessments they are developing. The field of exposure science is especially fertile at this moment and there are new examples every day of screening level exposure assessments for chemicals used in products to which consumers may be exposed. Currently, there seems to be some gaps in agency's ability to apply screening level assessments at the programmatic level and within the Guidelines. It is an area that should be addressed in greater detail in the Guidelines.

**EPA Response:** Text revised.

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**Location: Chapter 6**

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**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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 suggested 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, Tórnoro-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.

**EPA Response:** Text not revised for the discussion of model selection because EPA concluded that the current text addresses these points.

Pages 113 and 114 revised to include additional examples of fate and transport models for media other than air. The statement on page 115 has been revised to refer simply to Chapter 5.

References to relevant exposure models and exposure-PBPK models revised to include additional references in this section.

Text on page 16 where the concept of microenvironments is discussed has been revised to address this and other comments.

Text (page 118) has been added on this point.

The text on pages 118 and 119 regarding creatinine correction has been revised to address this and other comments. Correction of breast milk on the basis of percent lipids is already discussed in the text.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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](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.

**EPA Response:** Text not revised because the document emphasizes programmatic guidance and applications and EPA references (EPA 2014d and 2001g) are cited in the document.

Text not revised to address communication to the risk manager because this is identified in Section 6.1 (see bullet list) and chapter references.

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**Location: Chapter 6, Page 111, Box 6-3**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** Any references for guidance on fitting distributions to data?

**EPA Response:** Text not revised because, although this is a challenging issue for probabilistic modeling, addressing this issue is beyond the scope of this document.

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**Location: Chapter 6, Page 114, 5th paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** The Furtaw reference is 15 years old. Is it still relevant in this context? Even the Williams reference is six years old.

**EPA Response:** Text not revised because more recent publications on the same topic were not found based on Google and Google Scholar searches.



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**Location: Chapter 6, Page 116, 1st two bullets**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** 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?  
**EPA Response:** Text revised.

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**Location: Chapter 6, Page 116, Last paragraph**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** 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?  
**EPA Response:** Text revised.

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**Location: Chapter 6, Page 118, 1st paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** These are good examples.  
**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written section.

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 118, Table 6-2**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** I appreciate the addition of this table showing real-world examples of forward and reverse dosimetry.

**EPA Response:** Text not revised because comment compliments the technical panel on a well-organized and easily understandable table.

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**Location: Chapter 6, Section 6.2.2**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** 2. Page 107, Section 6.2.2, Level of model complexity. Only deterministic and probabilistic models are described in detail, while middle tier tools (i.e. advanced deterministic/mechanistic models) are not, although these were one of the elements in Figure 6-1. We suggest adding a discussion on this topic. The section on Advanced modeling methods (p.111) goes beyond conventional deterministic modeling covering more sophisticated techniques (e.g. micro-environmental exposure analysis, 2D MC). It would be helpful if some examples of Tier 1.5 tools were provided.

**EPA Response:** Text not revised because the commenter has identified a rather broad area of model refinement for deterministic models. Defining the characteristics of such models is difficult. This issue could be revisited in future updates of the document.

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**Location: Chapter 6, Section 6.2.3**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** 5. Page 113, Section 6.2.3 Categories of Models Used in Exposure Assessments:

- a. Simple PK Models: “Toxicodynamic” should be changed to “Toxicokinetic.”
- b. High Throughput Exposure Models: EPA should clarify that this project is not intended to refine the uncertainty in a risk assessment, but to more clearly interpret and integrate in vitro screening data for hazard assessment and subsequent risk characterization.

d. The only fate and transport models mentioned are both air models. There are many other models and a more balanced list of examples should be given.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** 6. Page 114, Section 6.2.3. ACC suggests acknowledging Integrated Fate/Transport-Exposure models (the non-US developments, e.g. Merlin Expo, Integra, IOM's IEAT).

**EPA Response:** Text not revised because of the level of effort that would be needed to confirm that guidance developed outside of the United States is consistent with EPA guidance (and terminology); the technical panel chose to not include references to international reports and projects in this document.

**Submitter:** CropLife America (CLA)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** Pg 119: "Important to note, however, is that although PBPK modeling can reduce uncertainty in internal dose estimates, reductions in uncertainty and increases in accuracy are not necessarily predetermined results."

Given the recent attention to the use of PBPK modeling, examples (and references) should be given for cases where use of PBPK models does not increase accuracy or decrease uncertainty.

**EPA Response:** Text revised.

**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** p. 118: Several examples of modeling organic chemical dose from biomonitoring data are included. Consider adding an example addressing the use of human inorganic metal biomonitoring data to assess body burden and tissue concentration. For example, Unice et al. 2015 evaluated the relationships between Co intake, cobalt human whole blood concentration, serum concentration, the serum protein bound fraction, and urinary excretion, body burden and tissue concentration.

**EPA Response:** Text revised to clarify that biomonitoring has been performed for a wide range of substances.

Text not revised to address other comments because the examples in the document are not intended to describe the range of substances that have been the subject of biomonitoring but to illustrate specific issues. Therefore, an example of each of the various types of substances is not required.

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**Location: Chapter 6, Section 6.3.4**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** If page 124 intends for health exposure assessors to support “a cost- benefit analysis that weighs the cost of additional analyses or data collection efforts versus the benefit of having a more refined exposure assessment,” EPA should provide examples of cost benefit analyses that do this. EPA should also indicate the guidance and policy documents that state the preferred method for such cost benefit analysis. Case studies demonstrating how EPA believes that appropriate cost tradeoffs should appear in scoping and refinements to the human exposure assessment would be very beneficial, but no examples are given in this draft.

**EPA Response:** Text not revised because this level of detail is beyond the scope of the document.

**Submitter:** CropLife America (CLA)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** \*\*Pg 124: “More recent and complex methods, however, apply the bootstrap-based uncertainty analysis technique, as described in Xue et al. (2006) for the SHEDS model application to the chromated copper arsenate case study.” How do the SHEDS model results compare to Monte Carlo methods?

Do more “complex” models translate to more realistic outcomes? How would this be evaluated?

**EPA Response:** Text not revised because the purpose of this document is to provide examples of models that illustrate certain categories. Providing details on the models’ predictions, their appropriateness for any given use and how they have been evaluated is beyond the scope of this document.

**Submitter:** CropLife America (CLA)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** Pg 124: “One of the key challenges for integrated fate/transport-exposure models is the quantification of coupled model uncertainties resulting from propagation of

errors from the different model components, which are linked during an integrated analysis.”

This requires additional explanation with examples and citations (the citation given is for one specific example and may not be broadly applicable).

**EPA Response:** Text not revised because the propagation of uncertainties is an important issue in complex models. However, the document is not meant to offer a complete discussion of all technical issues related to modeling. Thus, we believe that additional discussion of this point is beyond the scope of the document.

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**Location: Chapter 6; Chapter 8, Section 8.3.4**

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**Submitter:** Utility Water Act Group (UWAG)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** PRA is an important tool for EPA, the states, and the public to utilize in human exposure assessments and understanding the risks to human health. UWAG supports EPA’s inclusion of PRA in the Draft and its identification as an available tool when using modeling approaches for exposure assessments.

See Draft at 6.1, p. 103, and at 6.2.2., pp. 110-11; see also Draft at 8.3.4., pp. 155-56 (EPA identifies PRA as an available uncertainty[uncertainty] analyses that can be used to refine exposure assessments).

EPA has made statements in the past that appear inconsistent with the Draft. For example, in the context of disapproving water quality standards proposed by the state of Washington and EPA proposing its own revisions, 80 Fed. Reg. 55,063 (Sept. 14, 2015), EPA took the position that PRA is not an available tool to establish chronic human health water quality criteria. UWAG disagrees that PRA is not an available tool when establishing chronic human health water quality criteria and supports EPA’s position in the Draft that PRA should be used for human exposure assessments, which would include the use of PRA in the context of promulgating chronic human health water quality criteria under the CWA, if warranted. See, e.g., Draft at 6.2.3, pp. 114-20.

In the final document, given EPA prior statements that could be interpreted as inconsistent with the Draft, EPA should make it clear that it supports PRA for human exposure assessments. Further, it would be helpful if EPA identified the circumstances when PRA is an available tool and those circumstances that EPA believes it is not available, and provide the scientific rationale for those positions. In so doing, it also would be helpful if EPA identified examples when EPA has used (or approved of the use of) PRA for human exposure assessments, including related to the establishment of human health water quality criteria.

**EPA Response:** Text not revised because the purpose of the *Guidelines for Human Exposure Assessment* is stated in the Introduction and Executive Summary. It is not a policy document that defines or limits actions taken by individual EPA program offices.

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**Location: Chapter 7**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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 in 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 an 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.

**EPA Response:** Section 7.2.1 Budget and Logistical Planning. Text not revised because the text written in the section reflects the comment from the reviewer.

Section 7.3 Planning and Executing a Pilot Study. As recommended by the reviewer, a more current pilot study reference was added.

Section 7.3.2 Implementation Plan for the Full Study. Text not revised because providing case studies and lessons learned is beyond the scope of the document.

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**Location: Chapter 7, Page 128, Section 7.2**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** Citation list: perhaps it would help to provide a short (sentence-long bullet point or table entry) on each of these sources.

**EPA Response:** Text not revised because references are provided.

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**Location: Chapter 7, Page 129, Section 7.2.3, 2nd paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to include a more specific example.

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**Location: Chapter 7, Page 133, 4th paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because appropriate and relevant references are included.

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**Location: Chapter 8**

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<b>Submitter:</b>	American Chemistry Council (ACC)
<b>Topic:</b>	Uncertainty and Variability
<b>Comment Type:</b>	Public
<b>Comment:</b>	EPA should expand upon how using spatial and temporal variability influences the outcome. Examples where this is important and how the incorporation of temporal and spatial variability has changed outcomes would be useful. This concept also directly relates to time-activity patterns particularly when non-occupational receptors (people) will migrate throughout various geographic regions on a micro and macro scale at different aspects of time.
<b>EPA Response:</b>	Text revised.
<b>Submitter:</b>	CropLife America (CLA)
<b>Topic:</b>	Uncertainty and Variability
<b>Comment Type:</b>	Public
<b>Comment:</b>	<p><b>**Uncertainty in exposure assessments in epidemiology:</b> This issue is not specifically addressed in Chapter 8 but is an important issue. For example, Burns et al. (2014) note: "...with respect to exposure measurement error, Jurek et al. (2006) sampled papers from three epidemiology journals over 1 year and found that only 61% of the articles made any mention of exposure measurement error, and only 46% of those qualitatively described the possible effects. Only 1 of 57 sampled studies quantified the likely impact of exposure measurement error on results." They further state: "exposure misclassification is important to characterize in epidemiologic studies because it can distort exposure-response relationships and lead to biased or imprecise results."</p> <p>The authors provide a series of recommendations for improving exposure assessments in environmental epidemiology. This kind of information is valuable for exposure assessors and should appear in the Guidelines.</p>
<b>EPA Response:</b>	Text not revised because the comments and references pertain to the role of epidemiology in exposure assessment and are beyond the scope of this document.
<b>Submitter:</b>	Kenneth T. Bogen (Managing Scientist Exponent, Inc., Center for Occupational and Environmental Health Risk)
<b>Topic:</b>	References
<b>Comment Type:</b>	Public
<b>Comment:</b>	Bogen KT. Uncertainty in environmental health risk assessment: A framework for analysis and an application to a chronic exposure situation involving a chemical carcinogen. Doctoral Dissertation, University of California Berkeley, School of Public Health, Berkeley, CA, 1986.



Bogen KT. Uncertainty in Environmental Health Risk Assessment. Garland, New York, 1990.

Bogen KT. Methods to approximate joint uncertainty and variability in risk. Risk Anal 1995; 15(3):411-419.

Bogen KT. Risk analysis for environmental health triage. Risk Anal 2005; 25(5):1085–1095.

Bogen, KT. Unveiling variability and uncertainty for better science and decisions on cancer risks from environmental chemicals. Risk Anal 2014; 34(10):1795–1806.

Bogen KT, Spear RC. Integrating uncertainty and inter-individual variability in environmental risk assessment. Risk Anal 1987; 7(4):427–436. [Professor Robert C. Spear chaired Dr. Bogen's doctoral dissertation committee; see Bogen (1986) *supra*.]

Bogen KT, Gouveia FJ. Impact of spatiotemporal fluctuations in airborne chemical concentration on toxic hazard assessment. J Hazard Mater A 2008; 152(1):228–240.

Bogen KT, Cullen AC, Frey HC, Price PS. Probabilistic exposure analysis for chemical risk characterization. Toxicol Sci 2009; 109(1):4–17.

Bogen KT. Unveiling variability and uncertainty for better science and decisions on cancer risks from environmental chemicals. Risk Anal 2014; 34(10):1795–1806.

NRC. 1994. Science and Judgment in Risk Assessment. National Research Council (NRC), Committee on Risk Assessment of Hazardous Air Pollutants (1991–1994). National Academy Press, Washington, DC, p. 186. [Dr. Bogen served as a member of this NRC committee, which was established by Congress in the Clean Air Act Amendments of 1990.]

U.S. EPA. 1995. Guidance for risk characterization. U.S. Environmental Protection Agency, Science Policy Council, Washington, DC. Available online at <http://www.epa.gov/spc/pdfs/rcguide.pdf>

U.S. EPA. 2011. Exposure Factors Handbook: 2011 Edition. EPA/600/R-090/052F, September 2011. Chapter 2: Variability and Uncertainty. U.S. Environmental Protection Agency (EPA), Office of Research and Development, Washington, DC. Available online at <http://www.epa.gov/ncea/efh/report.html>

**EPA Response:** Text not revised because the references are not specific to exposure assessment.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** A little more information is needed to distinguish[distinguish] 1D from 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://www.epa.gov/modeling/sensitivity-and-uncertainty-analyses-training-module>). 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.

**EPA Response:** Text not revised because the purpose of this document is not to describe the specifics of any particular statistical method but rather to provide an overview and to make references to other documents that have greater detail. The commenter's recommendations for greater specificity are beyond the scope of this document.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to include additional references. A discussion on decision criteria for the use of uncertainty analysis across programs is too detailed for this document.

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**Location: Chapter 8, Page 141, 3rd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** Useful compilation of references for uncertainty in risk analysis.  
**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-presented list of references.

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**Location: Chapter 8, Page 143, Table 8-1**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Table 8-1 revised.

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**Location: Chapter 8, Page 147, Section 8.2.1**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** 1st bullet: Can you provide examples of when a quantitative analysis would or would not improve an assessment?  
**EPA Response:** Text revised.

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**Location: Chapter 8, Page 149, Section 8.2.3**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** It would be helpful if some results were given here.  
**EPA Response:** Text not revised because providing examples for all scenarios, methods, practices, etc., would significantly increase the length of the document.

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**Location: Chapter 8, Page 156, Role of Expert Elicitation**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** How does one quantify uncertainty? Are there some references to call upon here?  
**EPA Response:** Text not revised because Section 8.3.4 and Box 8-2 provide references to various techniques and documents where greater detail and examples are provided.

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**Location: Chapter 8, Sections 8.2.3 and 8.4; Chapter 9, Section 9.2.4**

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**Submitter:** CropLife America (CLA)  
**Topic:** Communication  
**Comment Type:** Public  
**Comment:** Communication: While this topic is addressed in section 9.2.4, it is also described in sections 8.2.3 and 8.4. These sections offers minimal information on methods for effectively communicating the extent of uncertainty and variability to different audiences, and the reader is referred to EPA guidance documents that are about 15 years old.  
Newer literature on this topic should be included (e.g., Fischhoff and Davis 2014; IOM 2013; Klopogge et al. 2007).  
**EPA Response:** Text not revised; the topic of communication of uncertainty in Section 8.2.3 also references the 2009 NRC report and appropriate EPA guidance. In addition, the text refers to Chapter 9 for additional information on communication.

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**Location: Chapter 9**

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**Submitter:** Nicole Cardello Deziel, Ph.D., MHS  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** 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.

**EPA Response:** Box 9.1 revised.

Content on dealing with the press/media removed from document.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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 from 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.

**EPA Response:** Text revised.

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**Location: Chapter 9, Page 167, Table 9-1**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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”?

**EPA Response:** Text not revised as references and URLs provide links to examples.

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**Location: Chapter 9, Section 9.1**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Communication

**Comment Type:** Public

**Comment:** 1. Section 9.1 should cite and discuss the IOM 2013 report on Environmental Decisions in the Face of Uncertainty.

Footnotes:

<sup>27</sup> <https://iom.nationalacademies.org/Reports/2013/Environmental- Decisions-in-the-Face-of-Uncertainty.aspx>

**EPA Response:** Text not revised; the document references *Environmental Decisions in the Face of Uncertainty* in several locations (e.g., Chapters 8 and 9).

**Submitter:** American Chemistry Council (ACC)

**Topic:** Communication

**Comment Type:** Public

**Comment:** 2. Page 160, second paragraph. The Seven Cardinal Rules of Risk Communication is mentioned but no reference is given. A reference is needed or the document should be included as an appendix.

**EPA Response:** Text revised.

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**Location: Non-specific**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** Should Provide More Attention and Discussion to Consumer Exposure Topics

A great deal of public discussion today about exposure to chemicals focuses on exposure from chemicals in consumer products as well as from other chemical uses (e.g. building materials, vehicles, electronics). These and other contemporary issues (e.g. home/office, home/workshop trends) are relevant to good exposure assessment design and much work has been accomplished on these topics.

Despite this increasing emphasis (both nationally and internationally) on understanding and estimating exposure to chemicals in consumer products, the

*Guidelines* contain only a cursory review of the topic. For example, in Chapter 5, Table 5.3, there is a row for consumer products but the primary emphasis is on food and drinking water, and from a monitoring perspective. There is no discussion of the importance of understanding exposure to consumer products and what to consider when conducting consumer product exposure assessments.

We recommend that EPA consider including greater discussion of consumer exposure topics in the context of both developments in the science of exposure assessment and specific guidance to practitioners. In particular, discussion of national and international initiatives, examples of how to conduct consumer product exposure assessments, available tools, and sources of data on chemicals in consumer products and consumer use patterns deserve attention in these *Guidelines*.<sup>8</sup>

Footnotes:

<sup>8</sup> See Appendix A for some examples of consumer product exposure assessment articles, models and initiatives for EPA's consideration and/or discussion.

**EPA Response:** Text not revised, as appropriate references to consumer products and information on EPA's role are provided.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** C. International Advances in Exposure Assessment Should Inform the *Guidelines*

There have been many new international advances in approaches to exposure assessment, including advances in the EU to address REACH requirements; advances in Canada; and developments in the OECD. ACC recommends that EPA consider these for inclusion in these *Guidelines*.

Many exposure tools and useful concepts have been developed in the EU. Examples include: the Generic Exposure Scenario concept, directly aligning exposure scenarios in modeling tools to use codes; exposure scenario templates for consistent reporting; extension of the occupational exposure and risk banding approach to consumer exposures; substantiated refinements to baseline default exposure scenarios (Specific Environmental Release Categories - SpERCs, Specific Worker Exposure Determinants- SWEDs, Specific Consumer Exposure Determinants - SCEDs); and tools such as the ECETOC TRA, AISE REACT, IH SkinPerm, EGRET, CHESAR, and others mentioned in EU REACH guidance documents.<sup>3</sup>

Tools and approaches have also been developed in Canada such as RAIDAR, ComET and CRAM.<sup>4</sup> We believe that acknowledging these advances would be informative and, if EPA has not evaluated these tools in detail, can be included in a way that does not necessarily equate to EPA endorsement.



Discussion of international activities aimed at increasing transparency and ease of data use across regions might also be useful in the Guidelines. These include development of OECD exposure scenario templates; the ongoing, not yet declassified OECD Internationally Harmonized Functional Use and Product Category Proposal; OECD development of a decision tree for when a child specific exposure assessment may be indicated;<sup>5</sup> and an OECD compendium of exposure models.<sup>6</sup>

Similarly, a range of international resources on general exposure factors have become available in the recent years, and their inclusion may be relevant and insightful for assessments that may need to consider socio-demographic differences which may impact exposure.<sup>7</sup>

Including advances in exposure science tools and approaches developed by other national/international agencies (e.g., EU, Canada, OECD) would strengthen the document as well as promote a greater level of international harmonization in exposure assessment. If EPA disagrees with this recommendation, at a minimum the Agency should make clear in these *Guidelines* that the omission of these references should not be interpreted as EPA disapproval of their use in informing exposure assessments conducted in the U.S.

Footnotes:

<sup>3</sup><http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>; <http://www.ecetoc.org/tra> ; [http://echa.europa.eu/documents/10162/13632/information\\_requirements\\_part\\_d\\_en.pdf](http://echa.europa.eu/documents/10162/13632/information_requirements_part_d_en.pdf); [http://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r15\\_en.pdf](http://echa.europa.eu/documents/10162/13632/information_requirements_r15_en.pdf); [http://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r16\\_en.pdf](http://echa.europa.eu/documents/10162/13632/information_requirements_r16_en.pdf) [http://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r14\\_en.pdf](http://echa.europa.eu/documents/10162/13632/information_requirements_r14_en.pdf)

CONCAWE. 2014. Specific Consumer Exposure Determinants (SCEDs) documents.

<https://www.concawe.eu/reach/specific-consumer-exposure-determinants-sceds-documents>;

A.I.S.E./FEA (International Association for Soaps, Detergents and Maintenance AISE REACT: Reach Exposure Assessment Consumer Tool. User Manual. <https://www.aise.eu/our-activities/product-safety-and-innovation/reach/consumer-safety-exposure-assessment.aspx>;AISE. products / European Aerosol Federation).

2015. A.I.S.E./FEA Specific Consumer Exposure Determinants (“SCEDS”). A.I.S.E. SCEDs Task Force.

Available: [https://www.aise.eu/documents/document/20150602150536-aise\\_sceds\\_factsheets\\_may2015\\_v1.pdf](https://www.aise.eu/documents/document/20150602150536-aise_sceds_factsheets_may2015_v1.pdf)

<sup>4</sup><https://www.trentu.ca/academic/aminss/envmodel/models/RAIDAR100.htm>

<sup>5</sup><http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=e>

nv/jm/mono(2014)29&doclanguage=en)

<sup>6</sup>[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=en/nv/jm/mono\(2012\)37&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=en/nv/jm/mono(2012)37&doclanguage=en)

<sup>7</sup>enHealth. 2012b. Australian Exposure Factor Guide. Environmental Health Committee (enHealth) of the Australian Health Protection Principal Committee, Australian Government Department of Health; Gamo M, Futatsumata M. 2006. Development of Japanese Exposure Factors Handbook. Epidemiology. 17: S528–S529. Available:

[http://journals.lww.com/epidem/Fulltext/2006/11001/Development\\_of\\_Japanese\\_Exposure\\_Factors\\_Handbook.1423.aspx](http://journals.lww.com/epidem/Fulltext/2006/11001/Development_of_Japanese_Exposure_Factors_Handbook.1423.aspx); Jang JY, Jo SN, Kim SJ, Kim S, Cheong HK. 2008. Development of Korean Exposure Factors Handbook.

Epidemiology 2008; 19: S214.

[http://journals.lww.com/epidem/Fulltext/2008/11001/Development\\_of\\_Korean\\_Exposure\\_Factors\\_Handbook.606.aspx](http://journals.lww.com/epidem/Fulltext/2008/11001/Development_of_Korean_Exposure_Factors_Handbook.606.aspx); Jang J-Y, Kim S-Y, Kim S-J, Lee K-E, Cheong H-K, Kim E-H, Choi K-H, Kim Y-H. 2014d. General Factors of the Korean Exposure Factors Handbook. J Prev Med Public Health. 47(1):7-17; Kim S, Cheong HK, Choi K, Yang JY, Kim SJ, Jo SN. Jang JY. 2006. Development of Korean Exposure Factors Handbook for exposure assessment. Epidemiology. 17(6) (Suppl):S460.

[http://journals.lww.com/epidem/Fulltext/2006/11001/Development\\_of\\_Korean\\_Exposure\\_Factors\\_Handbook.1235.aspx](http://journals.lww.com/epidem/Fulltext/2006/11001/Development_of_Korean_Exposure_Factors_Handbook.1235.aspx); Phillips LJ, Moya J. 2014 Exposure factors resources: contrasting EPA's Exposure Factors Handbook with international sources. J Expo Sci Environ Epidemiology. 24:233–43.)

**EPA Response:** Text revised, where appropriate. The number of international documents and references is limited because of the level of effort necessary to confirm that guidance developed outside the United States is consistent with EPA guidance (and terminology).

**Submitter:** American Chemistry Council (ACC)

**Topic:** Multiple – consumer product, exposure assessment; contribution of near-field and far-field exposure screening level approaches to exposure assessment; and data quality

**Comment Type:** Public

**Comment:** As noted in ACC's comments, the Guidelines include sparse or dated discussions on several important topics. In this appendix, we have provided a few examples to support this observation. These materials either provide more in-depth discussion or more up-to-date references than those covered in the Guidelines. Here, we have highlighted materials on consumer product exposure assessment; contribution of near-field and far-field exposure screening level approaches to exposure assessment; and data quality. This is not a comprehensive listing of all materials or all Guidelines topics in need of additional discussion or update. In its comments on the Guidelines, ACC recommends that EPA review the Guidelines references to ascertain whether in fact they represent the most up to date scientific perspectives

on these topics. As part of that recommendation, ACC also urges EPA to explore more recent sources for possible inclusion.

#### Consumer Exposure Assessment

There is increasing emphasis both nationally and internationally on understanding and estimating exposure to chemicals in consumer products. Unfortunately, the Guidelines include only a cursory review of this topic.

There is little discussion of the importance of understanding exposure to consumer products and what to consider in conducting consumer product exposure assessments. There are several topics that should be included in any guidance on exposure assessments to consumer products including national and international initiatives; examples of how to conduct consumer product exposure assessments, including available tools; and sources of data on chemical presence in consumer products and consumer use patterns.

Examples of initiatives that have been undertaken to develop an understanding of consumer products, habit and practices of use of the products by consumers and tools for estimating exposure include the following:

1. A brief discussion about the wealth of information already available regarding chemicals used in consumer products, the importance of understanding consumer behavior and using the information for ranking approaches is in:

Jayjock MA, Chaisson CF, Franklin CA, Arnold SF, Price PS. Using Publicly Available Information To Create Exposure And Risk-Based Ranking Of Chemicals Used In The Workplace And Consumer Products, *Journal of Exposure Science and Environmental Epidemiology* (2009) 19, 515–524.  
<http://www.nature.com/jes/journal/v19/n5/full/jes200843a.html>

2. Emissions, Exposure Patterns, Health Effects of Consumer Products (EPHECT) is a collaborative effort between Eurofin (Denmark and Germany), CEC-JRC, CEFIC, IPSOS (Belgium) and others to develop and implement research strategies for better understanding product use, determining parameters for consumer product exposure assessment and evaluating the use of this exposure assessment in policy making.

EPHECT will provide applicable tools to reduce the risk associated to the indoor use of consumer products.

(C. Dimitroulopoulou et al. 2015).

<https://sites.vito.be/sites/ephect/Pages/home.aspx> Science of The Total Environment, Volume 536, 1 December 2015, Pages 890–902 EPHECT II: Exposure assessment to household consumer products  
<http://www.sciencedirect.com/science/article/pii/S0048969715301935>

3. International Association for Soaps, Detergents and Maintenance Products (AISE) has also developed logic for screening and principles of consumer exposure assessment based on product use and consumer behavior. This illustrates the databases and information being developed by industry groups and made available to governments doing risk assessment. This will greatly inform “default values” and expand the horizons for easily accessible information

minimizing use of default values. <https://www.aise.eu/our-activities/product-safety-and-innovation/reach/consumer-safety-exposure-assessment.aspx>

4. Consumer Product Safety: Coherent Exposure Assessment for Multiple Products Containing Same Chemical Ingredients—Defining Exposure Opportunities for Different Consumer Types: Chaisson, Christine; Jayjock, Michael; Franklin, Claire; Diskin, Kerry *Epidemiology*: January 2011 - Volume 22 - Issue 1 - p S141  
[http://journals.lww.com/epidem/Fulltext/2011/01001/Consumer\\_Product\\_Safety\\_Coherent\\_Exposure.411.aspx](http://journals.lww.com/epidem/Fulltext/2011/01001/Consumer_Product_Safety_Coherent_Exposure.411.aspx)

This article discusses aggregation of multiple product exposures and focuses on development of categories of consumer behavior metrics which makes the assessments relevant to different consumer populations.

5. Surveys and Exposure Assessments for chemicals in multiple exposure consumer products have been completed by the Danish Ministry of the Environment/ Environmental Protection Agency (example below). These reports emphasize consumer behavior, product use, prioritization of products and uses to be considered, and notes sources for data on chemicals, products, use profiles, etc. Their principle for screening approach, “reasonable worst case”, is defined and applied.

Survey and Exposure Assessment of Methylisothiazolinone in Consumer Products

Survey of chemical substances in consumer products No. 134, 2015, The Danish Environmental Protection Agency Strandgade 29 1401 Copenhagen K Denmark [www.mst.dk/english](http://www.mst.dk/english), 2015, ISBN no. 978-87-93283-88-6.

6. RIVM, The Netherlands National Institute for Public Health and the Environment, Ministry of Health, Welfare and Sport, has summarized approaches and tools for “Consumer exposure to chemical substances,” including ECETOC TRA and ESIG, AISE, BAMA, CONSEXPO and other models and data with references and links to the details of those exposure assessment efforts. They also discuss how these approaches and tools can be used in a tiered approach.  
[http://www.rivm.nl/en/Topics/C/Consumer\\_exposure\\_to\\_chemical\\_substances/Exposure\\_models](http://www.rivm.nl/en/Topics/C/Consumer_exposure_to_chemical_substances/Exposure_models)

7. Dr. Yuri Bruinen De Bruin and colleagues provided an overview of the consumer exposure assessment approach as part of the REACH initiative and its application across chemicals of greatly varying use in the European market. Authors represent multiple EU organizations. Note: many other publications on these approaches are available. This reference provides a good foundation to the European work on exposure assessment and its application and evolution to date. *Journal of Exposure Science and Environmental Epidemiology* (2007) 17, S55–S66; doi:10.1038/sj.jes.7500587; published online 4 July 2007, “Risk management measures for chemicals in consumer products: documentation, assessment, and communication across the supply chain.”  
<http://www.nature.com/jes/journal/v17/n1s/abs/7500587a.html?free=2> 8. A.I.S.E. REACT: Reach Exposure Assessment Consumer Tool. (<https://www.aise.eu/our-activities/product-safety-and-innovation/reach/consumer-safety-exposure->

assessment.aspx) and in cooperation with Cefic, the HERA project (<http://www.heraproject.com/>) for developing approaches and tools for Human and Environmental Risk Assessment on ingredients of household cleaning products. 9. EGRET: European Solvent Industry Group Generic Exposure Scenario Risk and Exposure Tool. Zaleski, R.T., H. Qian, M. Zelenka, A. George-Ares, C. Money. 2014. *Journal of Exposure Science and Environmental Epidemiology* 24(1): 27- 35.

#### Far-Field Exposure Assessment/ Prioritization

One topic in human exposure assessment deserving more attention in the Guidelines is the importance of considering both near-field and far-field exposure in these assessments. Near-field exposures are the result of direct contact with the chemical through use of consumer products or other sources of chemicals in the immediate area of the humans, which is covered in part by the discussion on consumer product exposure. Far-field exposures are the result of human contact with chemicals in outdoor air, drinking water, and food as a result of general chemical use and release throughout the chemical life cycle and subsequent chemical fate and transport in the physical environment (air, water, soil, and sediment) and food web bioaccumulation. Both of these exposures are necessary to ensuring that all potential pathways of exposure are considered in any exposure assessment.

Much work has been done to develop tools, approaches, metrics for uncertainty, and databases for far-field exposure in the US, Canada and Europe which are not mentioned in this document. One of the prominent researchers in this area is Dr. Don Mackay who has published extensively on multi-media models for determining far-field exposure (e.g., Mackay 2001, and Arnot et al. 2010a). Arnot et al. (2012) presents a good introduction to the topic of far-field and application of this holistic approach to exposure within screening-level assessments. Example of far-field models that have been used in chemical assessments are RAIDAR (Arnot et al. 2006, 2008, 2010) and CalTOX (DTSC 1993a,b,c). Tom McKone of UC Berkeley has also emphasized the importance of considering regional, continental and global scales in determining exposure (McKone and MacLeod 2004). These are a few examples of far-field exposure approaches and models that should be included in the document:

Arnot JA, Mackay D, Parkerton TF, Zaleski RT, Warren CS. 2010b. Multimedia modelling of human exposure to chemical substances: the roles of biomagnification and biotransformation. *Environ Toxicol Chem* 29(1): 45-55.  
<http://onlinelibrary.wiley.com/doi/10.1002/etc.15/abstract>

Arnot JA, Mackay D. 2008. Policies for chemical hazard and risk priority setting: Can persistence, bioaccumulation, toxicity and quantity information be combined? *Environ Sci Technol* 42: 4648-4654.  
<http://pubs.acs.org/doi/abs/10.1021/es800106g>

Arnot JA, Mackay D, Webster E, Southwood J. 2006. Screening level risk assessment model for chemical fate and effects in the environment. *Environ Sci Technol* 40: 2316-2323.  
<http://ehp.niehs.nih.gov/1205355/>

Arnot, JA, Mackay D, Sutcliffe, R, Lo, B. 2010a. Estimating far field organic chemical exposures, intake rates and intake fractions to human age classes. *Environmental Modelling and Software* 25(10):1166-1175

#### Principles of Data Quality

ACC believes that a scoring system like Klimisch provides an objective standard of data quality that enhances transparency in assessments. ACC recommends that EPA include more discussion of approaches for evaluating the quality of data in the Guidelines and that as part of that discussion ACC include a reference to the Klimisch approach in its Guidelines. For example:

H.J. Klimisch, M. Andreae and U. Tillmann (1997): A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data, *Regulatory Toxicology and Pharmacology* Vol 25, pp 1-5, doi:10.1006/rtp.1996.1076, PMID 9056496  
<http://www.sciencedirect.com/science/article/pii/S0273230096910764>

**EPA Response:** Text not revised; the *Guidelines for Human Exposure Assessment* is a guidance document and not a literature review of methods and protocols. EPA acknowledges the numerous publications and emerging methods in areas such as data quality, exposure modeling and uncertainty assessment, among others. The Guidelines lays out methods and approaches used across EPA by its programs. Methods not employed by agency staff are generally not covered by this document.

Data Quality. Information on data quality is consistent with EPA's overall Data Quality System, including appropriate references.

Probabilistic Risk. References and information regarding probabilistic risk assessment are also updated.

Consumer products. Where appropriate, information is provided regarding consumer products regulated by EPA.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** These Guidelines should indeed "guide" future exposure assessments. To improve the usefulness of these Guidelines to the EPA program offices, as well as to the regulated community, ACC makes several recommendations:

The document is extensive and so would benefit from a "road map" of the document highlighting what is in the Guidelines, what has changed from the 1992 Guidelines, and how the document should be used;

The Guidelines suggest that many materials, concepts, models, etc. be "considered," but without significant direction as to which are the most important. EPA should clearly identify the "key considerations" for exposure assessments as part of this document;

EPA should review carefully all the documents, references, models, databases, etc. cited to ensure they are in fact up-to-date and reflect current exposure science practices and information. In this same vein, EPA should review each chapter to fill in any missing, significant references, and check to ensure its many hyperlinks are operational;

The Agency should delete Table 9-1 from the draft Guidelines

The Agency should provide more examples throughout the document; and EPA should update these Guidelines more frequently, e.g. every five years, or when a topical update is needed, in order to keep it current with new developments in both exposure and risk assessment.

**EPA Response:** Text revised and Table 9-1 deleted; references and hyperlinks updated.

**Submitter:** American Cleaning Institute (ACI)

**Topic:** Tiered Approaches

**Comment Type:** Public

**Comment:** The Guidelines should provide more actionable information about how one would begin developing their exposure and risk assessment. As an example, we point to the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) Risk Assessment in the 21st Century (RISK21) project<sup>6</sup> which included representatives from USEPA and the European Chemicals Agency on their Steering Team. In their 21st century roadmap for human health risk assessment, the RISK21 project provides a simple framework for modern risk assessment including an emphasis on problem formulation, exposure assessment, and tiered data development.<sup>7</sup> Their model uses the image of an inverted triangle to represent the level of complexity associated with lower-tier hazard and exposure assessment.

However, there is a great need to be able to screen out low risk situations using simple tools so that focus can be given to those substances requiring higher tiered, resource intensive risk assessment. We believe these low risk situations are common and we provided examples from our own experience above. We believe additional emphasis should be given to screening level exposure assessment and the application of appropriate tools to facilitate screening of low risk situations. We note there are some excellent examples of the application of screening level exposure (and risk) assessment by regulatory agencies with respect to chemical safety such as its use by the Government of Canada under its Chemical Management Plan. It appears that the best place within the Guideline for such information would be in Chapter 3 regarding Planning and Scoping and Problem Formulation. We note there is some discussion of these concepts in Chapter 6, Computational Modeling for Exposure Assessment on the use of deterministic models (pp. 108-110), however, we believe these concepts should be more foundational within the document.

Footnotes:

<sup>6</sup> <http://www.risk21.org/>

<sup>7</sup> Pastoor TP, Bachman AN, Bell DR, Cohen SM, Dellarco M, Dewhurst IC, Doe JE, Doerr NG, Embry MR, Hines RN, et al: A 21st century roadmap for human health risk assessment. *Crit. Rev. Tox.* 2014, 44:1-5.

**EPA Response:** Text not revised. The referenced document emphasizes many of the same principles outlined in the Guidelines, including: focusing on problem formulation, utilizing existing information, starting with exposure assessment (rather than toxicity), and using a tiered process for data development. Bringing estimates of exposure and toxicity together on a two-dimensional matrix provides a clear rendition of human safety and risk. The value of the roadmap is its capacity to chronicle the stepwise acquisition of scientific information and display it clearly and concisely. Many principles outlined in this paper and approach are already included in this document. The document was not included because it includes toxicity information that is outside the scope of this document.

**Submitter:** American Cleaning Institute (ACI)

**Topic:** References

**Comment Type:** Public

**Comment:** 1 Sanderson, H., J. Counts, K. Stanton, and R.I. Sedlak. 2006. Exposure and Prioritization—Human Screening Data and Methods for High Production Volume Chemicals in Consumer Products: Amine Oxides a Case Study. *Risk Analysis*, vol. 26(6): 1637-1657.

2 Veenstra, G., C. Webb, H. Sanderson, S.E. Belanger, P. Fisk, A. Nielsen, Y. Kasai, A. Willing, S. Dyer, D. Penney, H. Certai, K. Stanton, R. Sedlak. 2009. Human Health Risk Assessment of Long Chain Alcohols *Ecotoxicology and Environmental Safety*, 72:1016–1030.

3 Wibbertmann, A., I. Mangelsdorf, K. Gamon, R. Sedlak. 2011. Toxicological properties and risk assessment of the anionic surfactants category: Alkyl sulfates, primary alkane sulfonates and -olefin sulfonates. *Ecotoxicology and Environmental Safety*, 74: 1089-1106.

4 <http://www.cleaninginstitute.org/CPISI/>

5 81 FR 774 (January 7, 2016)

6 <http://www.risk21.org/>

7 Pastoor TP, Bachman AN, Bell DR, Cohen SM, Dellarco M, Dewhurst IC, Doe JE, Doerr NG, Embry MR, Hines RN, et al: A 21st century roadmap for human health risk assessment. *Crit. Rev. Tox.* 2014, 44:1-5.

8 WHO. 2008. Uncertainty and Data Quality in Exposure Assessment. Part 1, Guidance Document on Characterizing and Communicating Uncertainty in Exposure Assessment; Part 2, Hallmarks of Data Quality in Chemical Exposure Assessment. Geneva, Switzerland: IPCS Harmonization Project, WHO. <http://www.inchem.org/documents/harmproj/harmproj/harmproj6.pdf>.



**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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).

**EPA Response:** Text revised.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Consumer Specialty Products Association (CSPA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** CSPA recommends that for completeness the examples for differential exposure be expanded, (“Children have a higher exposure...”) and acknowledge that there are other situations in which exposure can be lower or that the external exposure can be similar but internal dose can be lower due to such factors as faster metabolism, excretion, etc.

**EPA Response:** Text revised.

**Submitter:** CropLife America (CLA)

**Topic:** References

**Comment Type:** Public

**Comment:** Burns CJ, Wright JM, Pierson JB, Bateson TF, Burstyn I, Goldstein DA, Klaunig JE, Luben TJ, Mihlan G, Ritter L, Schnatter AR, Symons JM, Yi KD. 2014.

Evaluating uncertainty to strengthen epidemiologic data for use in human health risk assessments. Environ Health Perspect 122:1160–1165.

Fischhoff B, and Davis AL. 2014. Communicating scientific uncertainty. *Proc Natl Acad Sci U S A*. 111 Suppl 4:13664-71.

Janesick AS, Dimastrogiovanni G, Vanek L, Boulos C, Chamorro-García R, Tang W, Blumberg B. 2016. On the utility of ToxCast<sup>TM</sup> and ToxPi as methods for identifying new obesogens. *Environ Health Perspect*.  
<http://dx.doi.org/10.1289/ehp.1510352>

Kloprogge P, van der Sluijs J, Wardekker A. 2007. Uncertainty Communication Issues and good practice. Report NWS-E-2007-199 ISBN 978-90-8672-026-2. Utrecht, Copernicus Institute for Sustainable Development and Innovation.  
[http://www.nusap.net/downloads/reports/uncertainty\\_communication.pdf](http://www.nusap.net/downloads/reports/uncertainty_communication.pdf) LaKind JS, Sobus JR, Goodman M, Barr DB, Fürst P, Albertini RJ, Arbuckle TE, Schoeters G, Tan Y-M, Teeguarden J, Tornero-Velez R, Weisel CP. 2014. A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-Lived Chemicals (BEES-C) Instrument. *Environment International* 73C:195-207.

LaKind JS, and Naiman DQ. 2015. Temporal trends in bisphenol A exposure in the United States from 2003-2012 and factors associated with BPA exposure: Spot samples and urine dilution complicate data interpretation. *Environ Res*. 142:84-95.

Lorber M, Koch HM, Angerer J. 2011. A critical evaluation of the creatinine correction approach: can it underestimate intakes of phthalates? A case study with di-2-ethylhexyl phthalate. *J Expo Sci Environ Epidemiol*. 21(6):576-86.

IOM (Institute of Medicine). 2013. Environmental Decisions in the Face of Uncertainty. Committee on Decision Making Under Uncertainty; Board on Population Health and Public Health Practice; Institute of Medicine.

Washington (DC): National Academies Press (US); May 20.

Maantay, J, Chakraborty, J, Brender, J. 2010. Proximity to Environmental Hazards: Environmental Justice and Adverse Health Outcomes. Strengthening Environmental Justice Research and Decision Making: A symposium on the science of disproportionate environmental health impacts. March, Washington, DC.

NRC. National Research Council. 2012. Exposure Science in the 21st Century: A Vision and a Strategy. Washington DC.

Nieuwenhuijsen MJ, Ed. 2015. Exposure Assessment in Environmental Epidemiology, Second Edition.

OECD. 2013. Guidance Document for Exposure Assessment Based on Environmental

Monitoring. OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 185.

<http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=en/v/jm/mono%282013%297&doclanguage=en>

Sauvé JF, Lévesque M, Huard M, Drolet D, Lavoué J, Tardif R, Truchon G. 2015. Creatinine and specific gravity normalization in biological monitoring of occupational exposures. *J Occup Environ Hyg.* 12(2):123-9.

Shacklette HT, and Boerngen JG. 1984. Element concentrations in soils and other surficial materials of the conterminous United States: U.S. Geological Survey Professional Paper 1270, 105 p.

USEPA. 1992. Guidelines for exposure assessment (EPA/600/Z-92/001. 57 Fed. Reg. 22888-22938, May 29). Washington, DC: Risk Assessment Forum, U.S. EPA. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=15263>.

USEPA. 2012. Radiation Protection Risk Assessment and Federal Guidance: Overview. U.S., EPA. Last modified February 9. <http://www.epa.gov/rpdweb00/rafg-overview.html>.

Weaver VM, Vargas GG, Silbergeld EK, Rothenberg SJ, Fadrowski JJ, Rubio-Andrade M,

Parsons PJ, Steuerwald AJ, Navas-Acien A, Guallar E. 2014. Impact of urine concentration adjustment method on associations between urine metals and estimated glomerular filtration rates (eGFR) in adolescents. *Environ Res.* 132:226-32.

WHO. World Health Organization. 2004. Biomarkers & Human Biomonitoring. Children's Health and the Environment WHO Training Package for the Health Sector; October. [www.who.int/ceh/capacity/biomarkers.pdf](http://www.who.int/ceh/capacity/biomarkers.pdf).

Xue J, Zartarian, VG, Ozkaynak, H, Dang, W, Glen, G, Smith, L, Stallings, C. 2006. A probabilistic arsenic exposure assessment for children who contact chromated copper arsenate (CCA)-treated playsets and decks, Part 2: Sensitivity and Uncertainty Analyses. *Risk Analysis* 26:533-541.

Yeh HC, Lin YS, Kuo CC, Weidemann D, Weaver V, Fadrowski J, Neu A, Navas-Acien A. 2015. Urine osmolality in the US population: implications for environmental biomonitoring. *Environ Res.* 3/22/2016:136:482-90.

**EPA Response:** Text revised.

**Submitter:** Earthjustice (Barbara Kerr)

**Topic:** Non-germane

**Comment Type:** Public

**Comment:** In fulfilling this hugely important responsibility, please do not overlook the impact on especially children's lives of the lead, asbestos, mercury, and other hazardous materials in the dust that can travel up to 400 feet (see HUD study) into the yards, gardens, and homes of neighbors when buildings are removed by mechanical demolition. Please immediately report to the nation how this threat can be stopped by an easy solution. Requiring deconstruction, disassembly with the purpose of reuse of the materials, can control the hazardous materials, while also minimizing carbon impact; saving natural resources especially trees; providing high quality

building materials especially old- growth lumber; creating entry level, good paying jobs; enabling low income people to afford to repair and maintain their homes rather than being displaced, and many other benefits to society.

Portland, Oregon just passed a resolution to mandate deconstruction for houses built in or before 1916 and houses designated historic IF they must be demolished. We are the first in the nation to do so. But on average, nearly every day a house is demolished and children exposed to the risk of brain damage all over our city.

We need the EPA to immediately release a statement that requiring deconstruction of all buildings subject to demolition can stop this. This one is so easy and can save so many.

**EPA Response:** Text revised to discuss lifestages.

Text not revised to include individual cases, which are program specific and outside the scope of the document.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text and figure revised.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because providing examples for all scenarios, methods, practices, etc., would significantly increase the length of the document.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** In addition, the document could provide enhanced utility with a few more examples or illustrations (specific suggestions noted in responses to charge questions).

**EPA Response:** Text not revised because providing examples for all scenarios, methods, practices, etc., would significantly increase the length of the document.

**Submitter:** The LifeLine Group

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Many existing references were incomplete, outdated or the links were not working. The references and discussion of exposure models of The LifeLine Group fall into this category. Our response to that omission is detailed in this response. We hope that the concepts of the contemporary models by The LifeLine Group will be included in the document with appropriate references. ...

The LifeLine Group strongly agrees that exposure assessment approaches and models must be capable of representing whatever population is relevant to the issue at hand. Data on which the assessment is based must be representative of that population and the model operations must utilize those metrics in their calculations. As noted on page 50 of the Guidelines, The LifeLine Group did develop a model, called Tribal LifeLine, with EPA support during the 2002-2008 period to address this very issue. The diets, lifestyles, daily activities and other lifestyle elements of tribal communities were not represented in exposure assessment models used by EPA. The work done and models developed as part of “Tribal LifeLine” were presented by Resek et al as correctly referenced in the Guidelines. That model and its underlying concepts was the precursor to the existing LifeLine models which are not cited in the Guidelines. Tribal LifeLine was replaced with a suite of models that can be used for dietary and non-dietary exposure assessment for tribal communities as well as for any other unique community or population group of interest. Those models are briefly described below. The models and detailed tutorials (some in Spanish as well) addressing the underlying scientific concepts and the operations of those models are (and have always been) freely available to any interested party via [www.thelifelinegroup.org](http://www.thelifelinegroup.org). Also importantly, data bases relevant to several unique communities have been developed by The LifeLine Group including five regions of Alaska, Southwestern America, First Nations and Inuit in Arctic Canada and Mexican- Influenced Communities. Those too are freely available.

### Descriptions of Available LifeLine Models: Dietary Record Generator©

Although it is virtually impossible to accrue contemporary, comprehensive and representative dietary intake data for all population groups, exposure assessments must be informed by data relevant to the population under consideration. Dietary intake surveys such as NHANES are expensive to conduct, and they age quickly given the dynamics of the food industry (global suppliers, restaurants, processed food products, ingredient substitutes, etc.). Dietary profiles must reflect specific population groups such as ethnically- influenced communities, tribal and arctic communities highly influenced by seasonal and food source parameters, communities depending on non- commercial food sources, specific cultural and socioeconomic subpopulations as well as those served in institutions, hospitals, care facilities, schools or other places where menu or food source diversity is confined. Actually, there is an abundance of information about diets and food sources, including information about what foods are eaten, by whom, in what seasons, the probability that such foods are eaten and when eaten, and how much is consumed. Some information is seasonally specific and/or age specific.

Unfortunately these data usually exist in atypical formats that are not amenable to use in existing modelling software that assesses exposure and risk. Unlike the national food surveys, the formats for most of this information is not ready for imbedding into existing dietary exposure models. Indeed, many existing dietary exposure models have US national dietary survey data imbedded into the model, making that data base the only information on which the exposure assessment can be based.

The LifeLine Dietary Record Generator™ (DRG™) is a stand software tool that accepts information from a wide range of sources about food and dietary habits and transforms them into simulated dietary files that can be imported into the LifeLine Customized Dietary Assessment Software© (CDAS) and Community Based Assessment Software© (CBAS) for exposure and risk assessment software. The DRG provides the opportunity to upgrade or amend existing dietary databases as better information becomes available, or food availability and habits change. The DRG also allows the use of dietary information relevant to unique population groups. The DRG is a probabilistic model and provides operational flexibility to the user.

### Activity Record Generator©

The Activity Record Generator© (ARG) is one component of the LifeLine™ suite of software that allows the user to evaluate potential dietary and non- dietary exposures and risks across a community or population. Once the activity information is entered, the ARG generates an activity profile, which is a simulation of the activities across the community or population. The activity profile file is then used in the Community Based Exposure and Risk Assessment Software© (CBAS) to investigate potential exposures and risks to the population of interest to substances of concern in the environment where these activities occur.

### LifeLine Customized Dietary Assessment Software©

The LifeLine Customized Dietary Assessment Software© (CDAS) allows the user to calculate dietary exposure and risks from unique diets. A unique diet could be any diet such as vegetarian diets, ethnic diets, low-carbohydrate diets, diets high in any specific food of interest or high in fortified foods, diets of subsistence foods, ethnically unique or provided by institutions (military rations for example). The first step in using the CDAS is to create a dietary intake profile for whatever foods are of interest using a separate tool called the LifeLine Dietary Record Generator© (DRG) which The DRG file is inserted into the CDAS for dietary exposure analysis and risk assessment which can be done on a seasonal basis, also accounting for periods of unusual consumption (e.g. vacation seasons).

Another feature of the CDAS™ is that it also allows a “menu blending” of diets, such as found in some populations that consume both commercial foods as represented in national surveys, and unique or atypical foods. The blending proportions can range from an all commercial diet through to an all unique diet.

#### LifeLine Community Based Assessment Software©

The LifeLine Community Based Assessment Software© (CBAS) is one component of the LifeLine™ suite of software that allows the user to evaluate potential exposures and risks across a community or population from dietary and non-dietary sources. The CBAS is designed to use unique dietary and activity files representative of a community or population and created using the LifeLine DRG and ARG respectively. Community specific dietary files, an activity file, and concentration and location of the substance of interest (often available in monitoring data) are needed in order to run the software. When such information is collected and entered into the CBAS, it is possible to investigate potential exposures and risks to the population of interest from substances of concern in the living environment and diet.

#### Conceptual Design

[See comment for Image]

We hope you'll correctly reference these models as part of your discussion about special population subgroups AND as you discuss human exposure models ( page 114 of the Guidelines) as the CBAS and CDAS are both human exposure models based on the same probabilistic methodology as contained in the original LifeLine models.

All models are authored by The LifeLine Group and available at [www.thelifelinegroup.org](http://www.thelifelinegroup.org) Tutorials and Data Bases as noted above are also available using that citation.

**EPA Response:** References were updated as requested. The descriptions of the software provided in the comment are not included because this document is not intended to provide detailed descriptions of available exposure software.

**Submitter:** The LifeLine Group

**Topic:** Data



**Comment Type:** Public

**Comment:** This topic is a very important, contemporary focus of exposure assessment. Health Canada, California and the EU have made significant contributions to the challenges inherent to understanding the way in which chemicals are used in consumer product formulation, consumer use of products and consequential exposures to the users. Much of the necessary information is being developed by industries and as part of REACH legislation in the EU. That entire field should be represented in the Guidelines if only as a rich source of information. There is a well established but still evolving approach involving product formulation, chemical use in product formulation, consumer behavior and product distribution and demographics of product purchase. Those concepts and others introduce some important aspects of exposure assessment for consumer products, including building construction materials, vehicles and other related products.

The LifeLine Group has discussed the rich supply of relevant data for consumer product exposure assessment in its publication,

Using Publicly Available Information to Create Exposure And Risk-Based Ranking Of Chemicals Used In The Workplace And Consumer Products by Michael A. Jayjock, Christine F. Chaisson, Claire A. Franklin, Susan Arnold and Paul S. Price. *Journal of Exposure Science and Environmental Epidemiology* (2009) 19, 515–524.

I hope that reference can be included in the Guidelines as it has served as a valuable reference for others considering the challenge of finding information relevant for human exposure assessment for chemicals in consumer products.

**EPA Response:** Text not revised because Chapter 6 provides guidance on selecting models.

Text not revised regarding Lifeline models due to inability to verify peer-review status. In addition, the model is designed to rank chemicals, which is beyond the scope of the guidelines.

**Submitter:** Virginia Department of Environmental Quality (DEQ)

**Topic:** Data

**Comment Type:** Public

**Comment:** Please include case studies and/or specific examples for the approaches, exposure calculations etc. described in this guidance. Possible examples could include how data in EPA's 2014 Updated Exposure Factors Handbook were derived or a site-specific case study. The inclusion of case studies could frame the information presented in the document and help guide researchers designing their own studies.

**EPA Response:** Text not revised because the exposure information used in the development of EPA's *Exposure Factors Handbook: 2011 Edition* is available.

## Tribal Concerns

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### Location: Chapter 4

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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. 50ff.) 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.

**EPA Response:** Text revised.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:**

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 lifestyles 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 lifestyles 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 lifestyles 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 population 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.

**EPA Response:** Text not revised because EPA agrees that socioeconomic status does not equate with increased sensitivity to agents to which they might be exposed. EPA has edited the document to draw a greater distinction between susceptibility (intrinsic biological factors) and vulnerability. The chapter is organized to start with the reason for considering lifestages, vulnerable groups and populations of concern in exposure assessment. Language in the chapter identifies situations where socioeconomic status could result in differential exposures (e.g., farm workers). The concepts are expected to apply to similar situations.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; no revision necessary because inclusion of policy documents and executive orders at the outset of the chapter provides context for consideration and lays out the rationale and considerations for identifying groups and lifestages. These documents can inform the problem formulation process. Although EPA acknowledges the disparity in numbers of children compared with individual cultural and ethnic groups, EPA has provided a number of existing policy statements and guidance documents related to lifestages compared with those groups.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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 differ 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.

**EPA Response:**

Text not revised because the purpose of this chapter is to inform assessors that when conducting planning and scoping and problem formulation, depending on the objectives, decision makers might need to consider these issues. The decision maker, in consultation with the assessor, decides if and how to apply these considerations. Other programs and guidance address the specifics. Executive Order 12898 has been added to the document.



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**Location: Chapter 4, Page 49, 1st bullet**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Some tribes are tied to fixed land bases; see text at bottom of p. 48.  
**EPA Response:** Text not revised because no specific recommended changes are provided.

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**Location: Chapter 4, Page 49, 2nd bullet**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “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.  
**EPA Response:** Text revised.

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**Location: Chapter 4, Page 49, 2nd paragraph**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** “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.  
**EPA Response:** Text revised.

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**Location: Chapter 4, Page 50, 1st bullet**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.



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**Location: Chapter 4, Page 50, 5th bullet**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 4, Page 50, last bullet**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text revised to include two references to support the bullet point.

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**Location: Chapter 4, Page 50, Models**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** Add Lifeline C-BAS (i.e., Tribal Lifeline)

**EPA Response:** Text not revised because the model was not added based on inability to verify peer-review status.

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**Location: Chapter 4, Page 51, Box 4-5**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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. Tribal Lifeline was included but needs to be updated to the current names.

**EPA Response:** Text not revised because the model was not added based on inability to verify peer-review status. Tribal Lifeline is included in the relevant section.

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**Location: Chapter 4, Page 51, last paragraph, lines 1-2**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** This sentence needs to be more direct, indicating who should become “familiar.”  
**EPA Response:** Text not revised because the assessor is identified as the individual who will be using the information and they need to become familiar with tribal culture.

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**Location: Chapter 4, Section 4.2**

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**Submitter:** Saginaw Chippewa Indian Tribe of Michigan  
**Topic:** Editorial  
**Comment Type:** Tribal (Public)  
**Comment:** Update to Section 4.2 (page 41) Regarding Vulnerability and Susceptibility in Exposure Assessment  
  
In section 4.2 near the bottom of page 41 it states:  
  
"Vulnerability includes economic, demographic, social, psychological and physical states of the receptor that influence patterns of exposure to environmental contaminants or alter the relationship between the exposure/dose of environmental contaminants and the health effect of the exposed individual or population (ATSDR 1997; deFur et al. 2007; US. EPA 2003d)."  
  
Although it is apparent later in the text that cultural differences can increase vulnerability of populations, there should be more clarification in this sentence in order to respect the cultural lifestyle of Tribes. This sentence should instead read as follows:  
  
“Vulnerability includes economic, demographic, social, cultural, psychological and physical states of the receptor that influence patterns of exposure to environmental contaminants or alter the relationship between the exposure/dose of environmental contaminants and the health effect of the exposed individual or population.”  
  
**EPA Response:** Text not revised because the definition of vulnerability is consistent with Agency use.

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**Location: Chapter 4, Sections 4.2 and 4.3**

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**Submitter:** Utility Water Act Group (UWAG)

<b>Topic:</b>	Lifestages, Vulnerable Groups and Populations of Concern
<b>Comment Type:</b>	Public
<b>Comment:</b>	<p>The Draft recognizes that tribal population and environmental justice concepts can and should be considered when assessing human exposure. This is true when promulgating human health water quality criteria under the CWA. The Draft correctly acknowledges that some tribal populations follow a subsistence-based lifestyle and have differential exposure based on fish consumption. See Draft at 4.2, pp. 42-43, 4.3.5, p. 49. The Draft explains that the scope and frequency of tribal population subsistence-based lifestyle needs to be determined because they are not accounted for in the general population and subsistence diets often include much higher-than-average quantities of fish or other game. See Draft at 4.3.5, p. 49. UWAG supports the Draft’s conclusion that tribal populations are to be treated as a “subpopulation” and not as a “general population” as tribal populations follow “unique traditional practices [including fish consumption] that are not included in ‘general population’ risk assessments.” Draft at 4.3.5, p. 49.</p> <p>Again, EPA in the past has made statements that are inconsistent with the Draft, also in the context of the state of Washington water quality standards action referenced above. 80 Fed. Reg. 55,063. In the Washington matter, EPA applied the fish consumption rates from tribal populations to develop state- wide human health water quality criteria. For fish-only water quality criteria, the tribal population consumption rates drive the derived exposure levels since they are substantially above the general population exposure level. This approach is in conflict with the Draft. The Draft aligns with EPA’s Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) (Human Health Methodology). EPA uses the Human Health Methodology as a guide when it develops or revises human health water quality criteria. The Human Health Methodology does not take the position that tribal populations should be considered the general population when developing human health water quality criteria under the CWA.</p> <p>In the final document, given the Agency’s prior statements that are inconsistent with the Draft, EPA should make it clear that tribal populations and environmental justice communities are subpopulations and are not to be considered the general population when developing human health water quality criteria under the CWA. This is consistent with EPA’s Human Health Methodology. EPA must address any concerns with tribal populations and environmental justice considerations within the restrictions of the applicable statutory and regulatory requirements and EPA guidance.</p>
<b>EPA Response:</b>	Text not revised because the document states that applicable statutory and legal requirements should be considered when conducting an exposure assessment (see Introduction to Chapter 3 and Section 3.1.4).

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**Location: Chapter 9, Section 9.4**

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**Submitter:** Saginaw Chippewa Indian Tribe of Michigan

**Topic:** Editorial

**Comment Type:** Tribal (Public)

**Comment:** Update to Section 9.4 (page 167) Regarding Communication Products and Strategies

Strategies in section 9.4 near the bottom of page 167 it states: "When appropriate, early and continuous communication with the community provides the opportunity for an exposure assessor to learn about the community's concerns, identify potential sources of exposure data, establish a relationship with local and state environmental and health agencies and work with local and state elected officials."

In order to respect the sovereignty and legitimacy of Tribal governments, Tribal elected officials, as well as Tribal environmental and health programs this sentence should instead read as follows:

"When appropriate, early and continuous communication with the community provides the opportunity for an exposure assessor to learn about the community's concerns, identify the potential sources of exposure data, establish a relationship with local, state, and Tribal environmental and health agencies and work with local, state, and Tribal elected officials."

**EPA Response:** Text revised.

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**Location: Non-specific**

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**Submitter:** Generally agreed upon by all reviewers

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because EPA has considered comments from the Tribal Council and public comments from individual Tribal Nations during the comment period.

**Submitter:** National Tribal Toxics Council

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Tribal (Public)

**Comment:** “The public ... expects EPA to make advancements in developing exposure (and risk) assessments that better reflect reality... Tools and methods are available and continue to be developed to incorporate these vulnerability factors in exposure (and risk) assessment and are being applied, particularly by academic researchers and some state agencies.” (pp. 39, para )There are no references here, and no attempt to provide perspective on how this work compares to the works being discussed. This whole chapter is out of date and does not reflect the considerable volumes of work done on this issue. Approaches about “unique exposure opportunities” and “vulnerable populations” are presented as issues only in working with tribes, but these are also prevalent in urban situations. NIH and CDC is leading the work on this yet there is no mention of that in this document. Meanwhile, the related citations which are provided are very old and represent a small part of the available work here. The work of “researchers and some state agencies” (pp. 39) seems dismissive and unimportant. Indeed, this is very important.

The World Health Organization’s 2006 document Environmental Health Criteria 237: Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals, regarding the proportional contributions of exposure to children does not reflect contemporary living in the United States or the mix of populations and living scenarios in the United States.

**EPA Response:** The purpose of this chapter is to make the exposure assessor and decision maker aware that exposure assessments need to consider lifestages, vulnerable groups and populations of concern. The development of the exposure assessment needs to be consistent with the planning and scoping and problem formulation steps identified in program specific guidance. While additional resources are provided, recommendations to coordinate with programs are also emphasized.

**Submitter:** National Tribal Toxics Council

**Topic:** Purpose and Scope

**Comment Type:** Tribal (Public)

**Comment:** In reviewing the U.S. Environmental Protection Agency (EPA or Agency) draft Guidelines for Human Exposure Assessment, three concepts are of particular concern for Tribal and ethnically dominant communities:

1. Principles underlying the concept of data quality,

2. the rules of peer review, and
3. making exposure assessment relevant to the communities of concern.

The Council's specific comments in relation to these overarching concerns are as follows.

1. The NTTC supports the role of exposure assessment as a decision making driver and risk mitigation guide even in the face of limited toxicology information. With decades between this draft Guidelines update and the first Guidelines publication in 1992, we applaud and thank the authors and contributors for the hundreds of hours of work conducted to create this draft. The 1992 Guidelines for Exposure Assessment was a modest beginning which legitimized exposure assessment as a component of EPA program thinking.

One of the most significant positive contributions made by this updated document is about the importance of exposure assessment – stated in the introduction and by inference throughout the document. This document represents a significant repositioning of the role that “exposure assessment” could play in the regulatory functions of EPA (or at least across many programs) and the maturing of the relatively new science of exposure assessment as compared to the long-standing “toxicology” component of risk assessment.

Optimistically, this document could have significant implications and encourage the improvement of the exposure sciences to serve the program thinking and Agency objectives. It is also an outstanding opportunity for all other stakeholders to contribute to the process by engaging the principles and providing information, perspective and credible thinking to address and improve on the exposure sciences. Most stakeholders cannot influence the pace of data production or interpretation of toxicology science, but there is great opportunity for all stakeholders to address the exposure assessment sciences, data and thinking. Even if this document does not permeate the thinking of other Agency offices, the overall statement in this document is a prize to quote when debating specific Agency decision-making that otherwise employs little of exposure assessments to inform their risk mitigation options.

**EPA Response:** Text not revised; no revision necessary because the commenters acknowledge the authors' work on the document.

**Submitter:** National Tribal Toxics Council

**Topic:** Data

**Comment Type:** Tribal (Public)

**Comment:** 2. The Council stresses the importance of including the contributions made by other EPA programs, Europe, Canada, the individual States, Universities and other stakeholders to Exposure Science regarding data, modeling, understanding principles of chemical use, developing libraries of activity patterns and many other principles not mentioned in the document. The document needs more attention given to exposure assessment principles which evolved in EPA program offices or

to data and approaches undertaken at the regional level. Some offices and regional programs have had extensive experience with many of the issues discussed in this document. EPA national and regional offices have funded relevant data, including that which is collected by tribes through these programs and efforts as examples: IGAP and Office of Water Quality grants and fellowships, Science to Achieve Results data, and the EPA Exposure Factors Handbook. The Guidelines need to reflect these resources, including a more specific citation, and discussion or attribution to those efforts. It is of utmost necessity to recognize the importance of REACH, EU modeling, and Health Canada's reviews on toxic chemicals because many of the principles, databases and models used and developed there will be fundamental tools for exposure assessment and risk mitigation strategies that industry will present to EPA. Canada's toxic substances review and principles developed for consumer products would be valuable to consider and acknowledge. There has been considerable work in states and in universities around the world on many of the issues mentioned. Existing references are dated and ignore recent developments and authors. Readers unfamiliar with these global advances could mistakenly believe that EPA is the only institution doing exposure assessment. Familiar readers may mistakenly believe that EPA is unaware of this other work. From a public relations perspective, this document is EPA-ORD centric and will likely seem narrowly focused to the many non-EPA scientists and global partners making outstanding contributions in this field and its regulatory applications.

These far-reaching sources and important works must at the very least be acknowledged as existing. Failure to acknowledge these works will suggest that EPA's approaches are inherently superior to others and put non- EPA thinking on the defensive. Health Canada's work with First Nations communities is another example not noted in the Guidelines. Also, the work of arctic communities in global scientific initiatives is not acknowledged.

**EPA Response:** Text revised.

**Submitter:** National Tribal Toxics Council

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Tribal (Public)

**Comment:** The entire conversation about Tribal communities and exposure, risk, data, etc. related to Tribal communities, other ethnic communities and socioeconomic communities must be rewritten. Within EPA itself, there are dozens of staff who work as Tribal liaisons, Tribal coordinators or other positions in frequent contact with Tribal and other unique communities. Their review and editing of Chapters 3 and 4 and perhaps the document overall would have significantly improved the discussion regarding Tribal communities and sensitive subpopulations. Additional EPA-related resources of information, counsel and data can be reached through EPA's multiple Tribal partnership groups, both office-specific, such as the NTTC, and overarching like the National Tribal Caucus and the National Tribal Operations Committee.

Note that Chapter 4 specifically addresses Tribal populations (section 4.3.5). Yet statements pertaining to “unique communities” in sections 4.3.6 (Other Racial and Ethnic Populations) and 4.3.7 (Socioeconomically Disadvantaged Populations) are relevant to Tribal and arctic communities as well.

The discussions reflect an elementary understanding of Tribal communities in terms of their Tribal lifeways, including diets, lifestyles, community management, and the federal trust responsibilities of EPA. “Tribal” seems to be a descriptor encompassing all groupings of Native American and Arctic communities, as well as our indigenous neighbors in Canada, Mexico/Central and South America. In discussion of collaboration with Tribal communities and utilization of risk assessment conclusions, the tone is condescending, and even at times disrespectful.

The Council is happy to revisit your document once these comments are addressed, to better convey a respectful and informed tone to Tribal peoples. As one example in the leading sentence to Section 4.3, the following is written, emphasis the Council’s:

Sections 4.3.1 to 4.3.7 present detailed discussions on exposure concerns for lifestyles (particularly children), tribal populations (e.g., American Indian, Alaska Native, other indigenous populations), other racial and ethnic groups...

Tribes are not a racial or ethnic group, but are indigenous peoples governing federally recognized sovereign nations. Use of the term “other” belies a fundamental misunderstanding of Tribes and could be construed by many Tribal peoples as ignorant.

In Section 4.3.5, it is written that Tribal communities may not accept proposed risk management solutions because they “may be unwilling to discontinue traditional practices that they consider essential to their existence” (pp 49). Yet this section does not note that the EPA does not yet require as the determinant for decision assembly the consideration of Tribal communities, or other “unique communities” in conducting their risk based decision making for registration of pesticides, nor in the consideration of consumer product exposure and risk assessment, national risk scenarios, water safety assessment, or any other major program utilizing “exposure and risk to the population”.

There is no mention of, or reference to, the ground-breaking document, Fish Consumption and Environmental Justice (2002), a report developed by one of EPA’s own federal advisory committees, the National Environmental Justice Advisory Council. This document is relevant to the Guidelines and would be educational for its authors in that it covers the impact of contaminated and depleted aquatic ecosystems on tribes, other indigenous communities, as well as other unique communities as described in the Guidelines. While the title and the report reference fish and aquatic resources, it actually encompasses all components and resources of aquatic ecosystems.

While fish may be a large component of some Tribal diets, it is not the only wild food consumed by all tribes. In this document, frequently, diet is portrayed as a function of eating fish. This inaccurately implies that when risk assessors understand fish consumption they’ll understand Tribal dietary exposure



assessment. No mention is made of the full varied range of subsistence diets, nor of the increasing contamination and bioaccumulation of marine mammals and grazing animals which are important parts of many unique community diets.

There is much known about the age, economic and seasonal influences on choices between western diet foods and subsistence/traditional foods in these communities. The blending of these diets for any given person is the norm (not one or the other) and the balance between those types of diets are influenced by many factors. Consideration of blended diets (both traditional and western) at different percentages by season and/or age can be quantified using the LifeLine Community Based Assessment Software. This was not noted in the text and is an important capability for exposure assessment models to have in order to appropriately reflect the possible exposures presented to people from their mixed diet—both traditional and western.

The reliability of “self-reported” information provided by members of Tribal communities is called into question. (pp 50) The NTTC considers this paternalistic and a gross misunderstanding of Tribal communities. Why would EPA consider self-reported information by Tribal members to be any less credible than self-reported information from any other community? What kind of evidence does this condemning conclusion draw on to warrant inclusion in a federal guidance document? Unfortunately, this reflects antiquated methods of survey-development and interactions with Tribal governments and communities.

In fact, we underscore that the comments in this entire section—Challenges in Conducting Exposure Assessments for Tribal Populations—require close examination and re-write. Why are any of these elements different for Tribal populations, as opposed to white suburban populations and other ethnic communities, etc.? After all, distrust of government agencies is not only represented in relationships with Tribal communities.

Exposure and risk assessments for these communities and the data needed for the assessments are discussed as almost a footnote to the “real risk assessments”. This may not have been the intention of the authors but surely this entire section deserves better construction for all of these topics. The uniqueness of “Tribal” communities and the resulting exposure and risk assessments are iconic of all communities who are, in one way or another, “unique”. The issues can be framed differently, noting the past limitations and the room for future improvement:

After decades of designing dietary consumption surveys and other exposure related data collection to include only non-Tribal participants, EPA has accrued volumes of information focused primarily on subpopulations that are not Native American, not socioeconomically challenged, and not ethnically dominant. Exposure and risk assessments, until fairly recently, used only models where those data were imbedded, making the assessments irrelevant to any subpopulations not represented in the data.

Fortunately, many strides were made in some areas with Tribal and other underserved communities that generated useful information or approaches for better exposure assessment where previously, EPA offices and scientists had little

truly collaborative work and distrust between the groups may have grown. These positive steps forward are not reflected in the discussion in the Guidelines. Examples of good data derived from Tribal and arctic communities (and from any other ethnically dominant community) for use in exposure assessments, and the processes used were not considered. This is a grave omission that could serve as important lessons for future emulation. These data include multiple works, include EPA-funded work some of which was previously referenced.

**EPA Response:** Text revised to be responsive to this comment. In addition, references were added.

**Submitter:** National Tribal Toxics Council

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Tribal (Public)

**Comment:** Examples of other sources of data and information:

The Council would like to include below relevant sources that should be cited and used in redrafting the Guidelines.

Regarding Tribal communities and resources, particularly in light of the treatment in the document of tribes as similar to minority communities, it would be fitting for the document to include a written definition that constitutes the unique legal status of American Indian Tribes, Alaska Natives, and Native Hawaiians:

- EPA's definition of Indian Country as defined at 18 U.S.C. § 1151: (a) all land within the limits of any Indian reservation under the jurisdiction of the United States Government, notwithstanding the issuance of any patent, and, including rights-of-way running through the reservation; (b) all dependent Indian communities within the borders of the United States whether within the original or subsequently acquired territory thereof, and whether within or without the limits of a state; and (c) all Indian allotments, the Indian titles to which have not been extinguished, including rights-of-way running through the same.

Regarding updated and relevant information on tribes and human health risk, this source was funded by the

U.S. EPA, the U.S. Department of Defense, the U.S. Department of Energy, and ITRC's Industry Affiliates Program:

- Interstate Technology & Regulatory Council. ITRC. 2015. Decision Making at Contaminated Sites: Issues and Options in Human Health Risk Assessment. RISK-3. Washington, D.C.: Interstate Technology & Regulatory Council, Risk Assessment Team. [www.itrcweb.org/risk-3](http://www.itrcweb.org/risk-3).

Regarding fish consumption and adequate and appropriate rates:

- Fish Consumption Rates Technical Support Document: A Review of Data and Information about Fish Consumption in Washington. Version 2.0 Final January 2013 Publication No. 12-09-058.

<https://fortress.wa.gov/ecy/publications/documents/1209058.pdf> Regarding Penobscot consumption of fish, turtle, and eel:

- The Penobscot River and Environmental Contaminants: Assessment of Tribal Exposure through Sustenance Lifeway. U.S. EPA Region 1, Regionally Applied Research Effort, Final RARE Report. August 2015.

<https://www.epa.gov/sites/production/files/2015-12/documents/final-rare-report-august-2015.pdf>

**EPA Response:** Text revised to include the document from Washington State.

Text not revised to include other references because the document emphasizes the importance of coordinating with programs for specific guidance.

**Submitter:** National Tribal Toxics Council

**Topic:** Data

**Comment Type:** Tribal (Public)

**Comment:** 3. Regarding Principles underlying the concept of data quality, introduce the concept of Relevance to be of equal weight to Precision/Uncertainty and Variability. The importance of relevance is imbedded in some of the document's discussions, but not recognized as a critical quality element.

Raising this principle to equal status with the statistical perspectives of precision/uncertainty and variability addresses many of the points discussed in the document, points about different environments, different scenarios, different populations, etc. Relevance also may be a driving element in any risk assessment's credibility thus, it should be explicitly cited, discussed and evenly ranked with Uncertainty and Variability. There are many examples of the importance of Relevance in contemporary exposure assessments. Data which is irrelevant, no matter how mathematically tidy, are not quality data. Data must describe the conditions and exposure opportunities of the people being exposed as a fundamental principle of quality. Variability and certainty are important, but secondary to the cornerstone of Relevance.

Until the importance of data Relevance is recognized, Agency decision making will continue to focus on databases that exclude Tribal and ethnically dominant communities. We recognize that Tribal community conditions, along with ethnically dominant and economically challenged "unique communities" bring "uncertainty and variability" to databases, rendering them less attractive and of lower quality to typical scientists or risk assessors. Also the data collection for these communities may be less standardized than historically utilized "national databases". Nonetheless, the standardized national databases exclude Tribal communities and under-represent ethnically dominant and underserved communities whose information may exist only in non-traditional formats and harvesting the information may require different techniques than employed by the traditionalist scientists at EPA who authored this report.

**EPA Response:** Text revised.

**Submitter:** National Tribal Toxics Council

**Topic:** Peer Review

**Comment Type:** Tribal (Public)

**Comment:** Expand the Principles of Peer Review to include the concept of relevance and expand the peer reviewer process to include people who can give credible, contemporary opinion on the concept of relevance of data (and approaches and models) used in an exposure assessment. The rules of peer review provided are incomplete and far too limiting as it relates to Exposure Science and its many issues, some of which are set forth, and some of which are omitted from the Guidelines. In this document, the definition of “peer review” (pp. 31) requires that the peer reviewers “are collectively equivalent in technical expertise to those who performed the original work”. This may leave no room for testimony of relevance or completeness of the data.

Rather, technical expertise can be viewed and measured as equivalent academic credentials, position within organizational hierarchy or such definitions. Examination of relevance of key exposure-related information may best reside with persons outside of the technical domains of the exposure assessor. For example, business owners understand product formulation, import/export dynamics over time, and factors defining product use which are critical to accurate and relevant exposure assessments about chemicals in commercial products. Such information is unlikely to be part of the knowledge base of most professional exposure assessors. Similarly, community elders and nutritionists may be “experts” on age-dependent activity patterns, traditional and pre-dominant food sources, and dietary profiles in their unique communities (Tribal, ethnically dominant, economically challenged, institutional living scenarios). Such information is unlikely to exist at all in the national databases and is easily overlooked or misunderstood by most professional exposure assessors.

Default values which have long been used in exposure assessments to represent the “typical US community” need revision and who better to make those observations than business owners, engineers, nutritionists, community elders, environmentalists, and other non-exposure assessment professionals. These “experts” may not have equivalent Western academic pedigrees to match the EPA’s exposure assessor, but they may know far more about the relevance of the assumptions, data, and defaults used in the assessment.

Indeed, this principle was formally presented to the EPA Science Advisory Panel and the Agency Risk Assessment Forum as part of the process used in developing the dietary profiles for Mexican-Influenced, Tribal and Arctic communities as part of the OCSPP Tribal Program (AKA OPPTS Tribal Program).

Additionally, the issue of “experts” and characterizing quantitative metrics for exposure and risk assessments were extensively studied as part of EPA’s Science Policy Council, publicly presented in January 2009 in its “Expert Elicitation Task Force White Paper,” and published in final form in 2011.<sup>2</sup>

The study was referenced by the authors of the Guidelines, but the Guidelines do not reflect the conclusions of the study. Expert elicitation – the process used extensively in science, engineering and research – is the synthesis of opinions of authorities of a subject where there is uncertainty due to insufficient data. The principles discussed in Expert Elicitation study enforces the concept that an expert must have extensive experience in the topic, but does not embrace the idea that they must compete with the credentials of the author of the exposure assessment. For all communities, but especially for the Tribal communities, it is necessary to employ Expert Elicitation principles to construct Relevant exposure assessments, starting with recognition of Relevant experts.

Compendia of Alaska Traditional and Subsistence Dietary Files, Compendium of Traditional Dietary Files for First Nations and Inuit in Arctic Canada, Compendium of Dietary Files for Mexican-Influenced Communities, Compendium of Dietary Files for the American Southwest, The LifeLine Group, 2004-2012, freely available at [The LifeLineGroup.org](http://TheLifeLineGroup.org).

US EPA Expert Elicitation Task Force White Paper, EPA Science Policy Council, Washington, DC, August 2011.

**EPA Response:** Text not revised because peer-review is discussed throughout the document, specifically in Sections 1.2, 3.1.4, 5.3.2 and 7.5. The *Peer Review Handbook, 4th Edition* is listed as a resource. Several parts of the Guidelines (Section 5.2.2, Box 8-1, Section 9.3.4) discuss expert elicitation and include references to guidance documents on the topic. Different approaches to peer review are conducted, as appropriate. EPA uses expert elicitation principles.

**Submitter:** National Tribal Toxics Council

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Tribal (Public)

**Comment:** Policy intersects “guidelines”. The priority for EPA (pp. 28) “premium” is placed on efficiency, cost efficiency, and cost-effectiveness and focus in the exposure assessment process”. Efficiency and quality also can be achieved by a willingness to adopt new ideas. Also, objectives of the modeling are set by schedule and budget of the office, presumably EPA (pp. 105 para 3), but these are probably not meant to apply to industry, academics or other stakeholders.

Consideration of the conceptual models, e.g., sources: This is an old and simplistic view. The example (runoff versus pipe) has little bearing on the principles of “sourcing” for the whole range of consumer products, housing, workspace, schools, etc. which are the sites for the major proportion of exposure opportunity. Though the simplistic view of “source” is still true, we now know significantly more about sources of chemicals entering into people’s environment and those principles are evolving and proving to be extremely useful. Chemical functionality in a product, is a great example. The collected lessons from REACH have changed the understanding of “source” and is a major contribution that needs to be acknowledged in this document. The collective work of Health Canada’s exposure

assessments on toxic substances would also be worth including as that has expanded the understanding of when a chemical is in the person's environment and under what circumstances. This is a key point, especially if the agency advocates for "tiered" exposure assessments using upper bound deterministic first cuts.

**EPA Response:** Text revised.

**Submitter:** National Tribal Toxics Council

**Topic:** Editorial

**Comment Type:** Tribal (Public)

**Comment:** Many of the citations are old, not accessible, incomplete, do not operate correctly, or do not reflect the most current references for the item being referenced.

**EPA Response:** All hyperlinks were checked and updated, as appropriate.

**Submitter:** National Tribal Toxics Council

**Topic:** Emerging Issues

**Comment Type:** Tribal (Public)

**Comment:** 6. Include current trends in exposure locations, and future targets. There is a complete omission of important issues in exposure assessment that will be targets for EPA attention in the near-future. These are issues which will impact global industry, trade, public health, consumer attitudes about product safety, regulatory decisions and possibly Congressional attention. Those include:

Nanomaterials. Among other reasons, Tribes' exposures are likely to be different due to the generally greater exposure to the natural environment and wider array of interactions with it.

Exposure from chemicals in consumer products, building materials, vehicles, electronics, foods, drinking water, and air quality factors. The discussion should include the latest thinking about global market dynamics of chemical use, functionality of chemicals in products, relationship to product pricing, distribution, and probability of a chemical being in one's close environment (home, school, workplace). These are contemporary issues relevant to good exposure assessment design and on which much work has been accomplished. Tribes have unique issues related here as well. Many Tribal peoples use products differently that is commonly the practice in non- Tribal communities, partly related to our unique lifestyles and customary practices. More accurate portrayals of exposure will benefit us.

Home/office, home/workshop trends: Today's reality is that the domains of home, office, and occupational work place are blurred by home-based industries and telecommuting. The document's citations about US activity patterns are outdated and possibly irrelevant in today's world, and certainly not useful for use in prospective analyses. The Guidelines never mention the limitations of these references. This changes everything in terms of the sourcing of chemicals into

homes, the assumptions about chemical controls (air venting, chemical supply control) and the populations expected to be exposed. Think about who is exposed when the small engine repair shop is now located in the garage or in the basement of the house. For Tribes, we have many, many small “mom and pop” shops, and other businesses that are under the radar and located in and next to our homes. The economically-depressed nature of most of our communities guarantees this trend will continue.

In this document, the pervasive context of people’s exposure opportunities is via commercial foods and community water, and activities in homes and offices, i.e., the urban/suburban paradigm as representative of US population. Ethnically strong communities, subsistence communities, rural or underserved communities are contextually a footnote to be treated as exceptions or outliers to the prescribed normative exposure assessment approaches.

**EPA Response:** Text revised.

**Submitter:** Utility Water Act Group (UWAG)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** UWAG writes separately to address a few issues that are important to UWAG. As discussed below, UWAG requests that EPA make clear how the final document will and should be used by EPA, the states, and the public as the agencies implement the various environmental statutory and regulatory programs focused on human exposure as they seek to set standards to protect human health, including the promulgation of human health water quality criteria as part of water quality standards under the Clean Water Act (CWA). In the Draft, EPA supports the use of probabilistic risk assessment (PRA) for exposure assessment. EPA also states that it supports treating tribal populations and environmental justice communities as subpopulations, as opposed to the general population, for purposes of assessing human exposure. In other contexts, EPA has taken positions that conflict with these statements. In the final document, EPA should make it clear that it supports the use of PRA and the treatment of tribal populations and environmental justice communities as subpopulations.

**EPA Response:** Text not revised because the document recommends coordination with the appropriate EPA program for specific guidance on the development of exposure assessments under legislative mandates.

Chapter 6 of the document provides a process and guidance for determining when to use probabilistic methods using a tiered approach. Specifically stating that a probabilistic risk assessment needs to be conducted to support all decisions is beyond the scope of this document.

## Other Comments, Location-Specific

### Chapter 1. Introduction

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**Location: Chapter 1, Page 1, 1st Paragraph, 2nd sentence**

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**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 1, Page 2, 3rd paragraph, line 1**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “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...”

**EPA Response:** Text revised.

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**Location: Chapter 1, Page 2, 4th paragraph, line 1**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “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.”

**EPA Response:** Text revised.

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**Location: Chapter 1, Page 3**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Editorial



**Comment Type:** Peer Review  
**Comment:** This page is redundant with text  
**EPA Response:** Text revised.

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**Location: Chapter 1, Section 1.1**

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**Submitter:** American Chemistry Council (ACC)  
**Topic:** Editorial  
**Comment Type:** Public  
**Comment:** Page 1, revise sentence as follows: “The Agency needs to understand whether the agent can cause an adverse health effect, at what level the effect may be seen, and if necessary, how exposure to the agent could be reduced.”  
**EPA Response:** Text revised.

## **Chapter 2. Principles of Exposure Science/Exposure Assessment**

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**Location: Chapter 2**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** 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.

**EPA Response:** Text not revised because the relative source contribution decision tree is specific to one program and legislative mandate.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the focus of this document is on human exposure to chemical agents in the non-occupational environment as stated in the Executive Summary and Chapter 1.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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 Liou 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 appropriately 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  $<2.5\mu\text{m}$  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).

**EPA Response:** Text not revised because this chapter is designed to provide an overview.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the TEAM Study is highlighted in Section 2.5, Section 3.3, Table 5.5, Box 7-1 and Section 7.3 with references.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because Section 2.1, paragraph 3 discusses the "duration of contact of the contaminant with the receptor." The text describes toxicity as "the endpoint for exposure science is the dose at the target internal tissue, organ or developing the dose the embryo/fetus receives: the location where the dose initiates the toxicity pathways that trigger the adverse effect. This endpoint serves as the starting point for toxicology (Pleil and Sheldon 2011)."

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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-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 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 stacks). 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.

**EPA Response:** Text not revised because discussion of the precautionary principle is beyond the scope of this document. The discussion of evaluating exposure distributions is found in Section 5.4.4 and includes a citation to the 2004 Office of the Science Advisor Staff Paper Risk Assessment Principles and Practices.

Uncertainty and variability are discussed in Chapter 8 of the Guidelines.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because mixture assessment is mentioned for completeness. Section 2.3.3, under the subtitle Single Chemical versus Aggregate versus Cumulative Exposures, provides a discussion of mixture assessments with citations.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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 [are] 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.

**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter and recognizes a more detailed discussion of uncertainty and variability provided in Chapter 8.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

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.

**EPA Response:** Text not revised because the presentation of the source-to-effect graphic in Chapter 2 is to demonstrate the position of exposure in the risk assessment

paradigm. As noted in the document, however, the focus of this document is on exposure.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Emerging Issues

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** An emerging issues section was added in Chapter 2 (Section 2.6). The topics mentioned in the comment have been added in Section 2.6.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Data

**Comment Type:** Peer Review

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

**EPA Response:** Text not revised because this document addresses exposures to chemical agents independent of intended use.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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=en/v/jm/mono\(2013\)7&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=en/v/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.

**EPA Response:** Text revised.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because specific recommended revisions are not provided.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Aggregate and Cumulative Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because specific recommendations for edits are not provided.

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**Location: Chapter 2, Line 18, last paragraph**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** Need a better description of the different mechanisms of dermal exposure.

Also need citations for the statements regarding contributions gases and aerosols.

**EPA Response:** Text revised in Section 2.4.3 to include examples of ways that chemicals can contact the skin. Citation added as suggested by commenter.

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**Location: Chapter 2, Page 10, below table**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “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...”

**EPA Response:** Text not revised because EPA concluded that once an agent has crossed the external surface, it has entered the body.

---

**Location: Chapter 2, Page 11, 1st paragraph**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** Bioavailability of metals from soil is also affected by the significant pH changes along different parts of the GI tract

**EPA Response:** Text not revised because Section 2.2.2 discusses bioavailability of metals in soils.

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**Location: Chapter 2, Page 11, line 1**

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**Submitter:** Alan H. Stern, Dr. P.H., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** After, “chemical characteristics of the soil,” add, “and the characteristics of the physical and chemical interactions of the specific metal and the specific soil.”

**EPA Response:** Text revised.

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**Location: Chapter 2, Page 11, top**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** Delivered dose: is “amount” expresses in mass, mass per unit body weight, or mass per unit BW per unit time?

**EPA Response:** Text not revised because Section 2.4 provides example equations.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.)

**EPA Response:** Text not revised because the focus of the document is on exposure and not toxicity assessment.

---

**Location: Chapter 2, Page 12, 2nd paragraph, lines 5-9**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the scope of the assessment is determined in the planning and scoping and problem formulation step of the exposure assessment.

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**Location: Chapter 2, Page 12, top**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Note for the figure should stay on previous page.  
**EPA Response:** Formatting revised.

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**Location: Chapter 2, Page 13, 5th paragraph, line 4**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** “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.  
**EPA Response:** Text revised.

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**Location: Chapter 2, Page 13, last paragraph, 2nd sentence**

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**Submitter:** Michael A. Jayjock, Ph.D., CIH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised because indirect methods (such as modeling) are discussed in the same paragraph after the discussion of direct methods.

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**Location: Chapter 2, Page 13, Section 2.3.2**

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**Submitter:** Michael A. Jayjock, Ph.D., CIH  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** 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-response or dose-response data (often from animal studies) to estimate risk.  
**EPA Response:** Text revised for clarity.

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**Location: Chapter 2, Page 13, Section 2.3.3, 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** The last sentence is a good synopsis of the value of exposure assessment. This could be developed further.

**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter.

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**Location: Chapter 2, Page 14, 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 2, Page 14, Table 2-**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** What about exposures to multiple compounds with different toxicological endpoints?

**EPA Response:** Text not revised because the document references guidance on chemical mixtures in Section 2.5.

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**Location: Chapter 2, Page 16**

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**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Typo floating “, respectively”

**EPA Response:** Text revised.

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**Location: Chapter 2, Page 16, 1st line**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** Does a probabilistic approach “depict” uncertainty? Could change to say it accounts for uncertainty or addresses uncertainty.

**EPA Response:** Text revised.

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**Location: Chapter 2, Page 16, 2nd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Aggregate and Cumulative Exposure Assessment

**Comment Type:** Peer Review

**Comment:** Single-chemical versus aggregate-both are single chemical. Single pathway may differ from aggregate if multiple pathways are of interest.

**EPA Response:** Text not revised because the text below Figure 2-2 and Table 2-1 provide definitions of aggregate consistent with the comment.

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**Location: Chapter 2, Page 16, 2nd paragraph, lines 1-7**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Aggregate and Cumulative Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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)

**EPA Response:** Text not revised because terms are defined upon first use in the document, and definitions are consistent with EPA use with support from the scientific literature (for example, Zartarian et al., 2005, 2007).

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**Location: Chapter 2, Page 16, 3rd paragraph, Lines 1-3**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Aggregate and Cumulative Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the comment lacks specific recommendations for editing the document.

---

**Location: Chapter 2, Page 16, 4th paragraph (first in Section 2.3.4), line 4**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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...”?

**EPA Response:** Text revised.

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**Location: Chapter 2, Page 16, top**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** Discussion of analytical versus empirical distributions is warranted.

**EPA Response:** Text revised in Section 2.3.3 Approaches for Exposure Assessment to show that point estimates and empirical distributions are the same and that analytical distributions and statistical approaches are the same.

---

**Location: Chapter 2, Page 17, 4th paragraph, line 1**

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**Submitter:** Alan H. Stern, Dr. P.H., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “(discrete form)” here is not explained.  
**EPA Response:** Text revised.

---

**Location: Chapter 2, Page 17, 4th Paragraph, line 4**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** Has the Draft Protocol ever been finalized as such? Or, has it been integrated into the SHEDS-Residential model?  
**EPA Response:** Text not revised because the Draft Protocol was published with the word draft in its title.

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**Location: Chapter 2, Page 17, last paragraph**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** When “inhalation exposure is assumed to equal dose” is this “uptake dose” or “intake dose”  
**EPA Response:** Text not revised because the relationship between exposure and dose are shown in Figure 2-3.

---

**Location: Chapter 2, Page 17, Section 2.4.1**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** Inhalation exposure is assumed equal to dose—Where? At the lungs? At the mouth/nose?  
**EPA Response:** Text not revised because the statement is taken out of context.



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**Location: Chapter 2, Page 18, 1st line**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** “Complicated”—but earlier in the paragraph the text says that in many cases dose is simply assumed to be equal to exposure.  
**EPA Response:** Text not revised because the statement is taken out of context.

---

**Location: Chapter 2, Page 18, 2nd equation**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised because unit conversion will change the units appropriately.

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**Location: Chapter 2, Page 18, equation**

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**Submitter:** Michael A. Jayjock, Ph.D., CIH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:**  $E_{inh}$  = inhalation exposure (mass per time) [Over the duration of exposure]  
**EPA Response:** Text not revised because the document identifies the equation describing inhalation exposure as the simplest form of the equation along with appropriate references.

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**Location: Chapter 2, Page 19, 3rd paragraph**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** 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.

**EPA Response:** Text not revised because the text indicates this is a general equation and appropriate references are provided in Chapters 2 and 6.

---

**Location: Chapter 2, Page 19, center of page**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because Section 2.4.3 includes the following references:  
Dermal permeability coefficients are available in the referenced document *Dermal Exposure Assessment: A Summary of EPA Approaches* (U.S. EPA 2007d).  
*Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment)* (U.S. EPA 2007c) and ExpoBox (dermal).

---

**Location: Chapter 2, Page 19, equation**

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**Submitter:** Alan H. Stern, Dr. P.H., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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).

**EPA Response:** Text not revised because references to dermal guidance documents are provided.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** Is a mono-layer assumed?

**EPA Response:** Text not revised because references in the section refer to the *Risk Assessment Guidance for Superfund Part E*, which includes a discussion of the mono-layer.

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**Location: Chapter 2, Page 20, Box 2-1**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** OPP also has tools/methods for conducting occupational exposure assessment for mixers, loaders, handlers, applicators. Cite them here, too.  
**EPA Response:** Text not revised because Chapter 1 states this document focuses on human exposure to chemical agents under non-occupational scenarios so the recommended references are not appropriate for inclusion.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** 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>  
**EPA Response:** Text in Box 2-1 revised.

---

**Location: Chapter 2, Page 21, 2nd bullet**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Add “principles of exposure assessment”; this is a key component of the document cited.  
**EPA Response:** Text revised.

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**Location: Chapter 2, Page 4, 1st paragraph**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

---

**Location: Chapter 2, Page 4, 1st paragraph, lines 1-4**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** This sentence matches over 15 words from Barr, 2006; therefore, it should be in quotation marks.

**EPA Response:** Text not revised because EPA verified the text from Barr et al. (2006) is not duplicated and therefore does not require quotation.

---

**Location: Chapter 2, Page 4, Section 2.1, 2nd paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “the committee.” What committee? Does this refer to the NRC?

**EPA Response:** Text revised.

---

**Location: Chapter 2, Page 5, 1st paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** It should be stated that the endpoint for exposure may be different for different effects despite identical exposure

**EPA Response:** Text not revised because the text indicates this is the starting point.

---

**Location: Chapter 2, Page 5, bottom**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** What are “changes in human and natural factors?”

**EPA Response:** Text not revised because the factors are listed in the text box to the left of the box including upstream human and natural factors.

  

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** “actions or events might be sources of stressors...” Actions or events might also be stressors themselves.

**EPA Response:** Text not revised because the sentence recognizes that “... actions or events might be sources for stressors that cause changes in both human and natural factors or that alter human behaviors or both.”

---

**Location: Chapter 2, Page 5, Figure 2-1**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because non-chemical stressors are defined as factors found in the built, natural and social environments, including physical factors such as noise, temperature and humidity, and psychosocial factors (e.g., poor diet, smoking). Cumulative risk assessments include both chemical and non-chemical stressors by definition. Tulve NS, Ruiz JDC, Lichtveld K, Darney SP, Quackenboss JJ. 2016. Development of a conceptual framework depicting a child’s total (built, natural, social) environment in order to optimize health and well-being. *Journal of Environment and Health Sciences* 2(2):1-8. Rider CV, Dourson M, Hertzberg RC, Mumtaz MM, Price PS, Simmons JE. 2012. Incorporating nonchemical stressors into cumulative risk assessments. *Toxicological Sciences, Society of Toxicology* 127(1):10-7.

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**Location: Chapter 2, Page 5, line 9**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** exposure—here refers to exposure at the boundary of the body; you might want to specify that.

**EPA Response:** Text not revised because the text refers to “the receptor’s external exposure surface,” which is a boundary. Boundary is discussed in the definitions (Section 2.2.1).

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**Location: Chapter 2, Page 6, 2nd paragraph**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “Exposure science is developing methods...” I suggest changing this to indicate that scientists are doing this, not science itself.  
**EPA Response:** Text revised.

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**Location: Chapter 2, Page 6, Figure 2-2**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** Circle says “sources.” Sources of what?  
Define “Environmental Intensity.”  
Do the various colors (sometimes matching, sometimes not) mean anything? 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?  
**EPA Response:** Text not revised because Figure 2-2 is adapted from the NRC report and the supporting text to the figure states this. More details can be found in the NRC report referenced in the text.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** It’s hard to read the words in red on grey and white on orange, even if you enlarge the page to 150%.  
**EPA Response:** Text not revised because Figure 2-2 is adapted from the NRC report and the supporting text to the figure states this. More details can be found in the NRC report referenced in the text.

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**Location: Chapter 2, Page 6, last paragraph, line 1**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the text is correct as written.

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**Location: Chapter 2, Page 9, Table 2-1**

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**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Exposure point: The location [in space and on the body] at which the receptor comes in contact with the agent.

**EPA Response:** Text not revised because the definition is consistent with EPA use.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** Add “stressor”

**EPA Response:** Text revised.

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**Location: Chapter 2, Pages 10-11, bottom 10, top 11**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** Is there a citation for the statement on the bioavailability of metals? (Or is it the EPA 2007I mentioned in the statement about lead?)

**EPA Response:** Text not revised because the 2007 guidance document is limited to evaluating the bioavailability of metals ingested in soil or other soil-like media, and not for all media for the purpose of assessing human health risks.

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**Location: Chapter 2, Section 2.1**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Figure 2-1: Transport and transformation processes include degradation, chemical reaction and partitioning. These needed to be added here and in the text.

**EPA Response:** Figure 2-1 revised.

  

**Submitter:** American Chemistry Council (ACC)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** Page 7: “All important parameters for describing human exposure cannot be identified and known in detail because of the nature of working in an open system.” This statement is unclear. Is EPA saying that uncertainty for any exposure data set is too uncertain to be used with confidence in any number of chemical safety assessment endeavors? EPA should specify the quality of exposure information, e.g., fit for purpose objectives, and not include an open statement that would tend to limit the use of any exposure information.

**EPA Response:** Text revised.

  

**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Figure 2-3: The diagram should be modified to show that metabolism can occur by the barrier tissue, not just after passage.

**EPA Response:** Figure 2-3 revised.

  

**Submitter:** The Teratology Society

**Topic:** Editorial

**Comment Type:** Public

**Comment:** In Chapter 2 (page 5), the processes important for exposure science note that “exposure becomes a dose when the contaminant moves across the receptor’s external exposure surface and is absorbed into the body...The endpoint for exposure science is the dose received by the target internal tissue or organ: the location where the dose initiates the toxicity pathways that trigger the adverse effect.” Awareness of prenatal exposure considerations might be greater if the following additional wording were included, “The endpoint for exposure science is the dose received by the target internal tissue, organ or developing embryo/fetus: the location where the dose initiates the toxicity pathways that trigger the adverse effect.” A similar small change could be provided on page 7, “Behaviors relative to



lifestage can be particularly influential determinants for exposure particularly for infants and toddlers, and for the embryo/fetus during pregnancy.”

**EPA Response:** Text revised.

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**Location: Chapter 2, Section 2.3.4**

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**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** p. 16: The statement is made that “[T]he most critical factors that influence the exposure estimates are the ability to capture adequately inherent variability in model inputs and parameters...” It is recommended that this statement be revised with a reference provided or the statement be deleted because it diminishes the importance that model selection uncertainty and parameter uncertainty can have on exposure assessments. In some cases, model selection uncertainty or parameter uncertainty (which are reducible by further study) may be more important factors than inherent variability. In addition, determination of critical factors depends on scale. The critical factors for an individual risk estimate is different than that of a population.

For example, in an individual, uncertainty about renal function, renal resorption, and protein binding may be the largest contributors to refining an internal dose estimates, but in a population both variability and uncertainty in renal function would need to be considered. If an important mechanism such as renal resorption or protein binding is ignored, model uncertainty may far outweigh variability.

**EPA Response:** Text revised.

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**Location: Chapter 2, Section 2.4.1**

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**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** p. 17. In Section 2.4.1, the exposure equation  $E = Ca \times IR$  is presented. It is recommended that the preference for the concentration of the chemical in air as the exposure metric expressed in RAGS F and the Inhalation Dosimetry Methodology be explained in the text or a footnote (EPA, 1994; 2009).

RAGS F notes:

The Superfund Program has updated its inhalation risk paradigm to be compatible with the Inhalation Dosimetry Methodology, which represents the Agency's current methodology for inhalation dosimetry and derivation of inhalation toxicity values. This document recommends that when estimating risk via inhalation, risk assessors should use the concentration of the chemical in air as the exposure metric (e.g.,

mg/m<sup>3</sup>), rather than inhalation intake of a contaminant in air based on IR and BW (e.g., mg/kg-day).

**EPA Response:** Text not revised because citations are provided to RAGS Part F (USEPA 2009f).

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the equation is correct as written.

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### **Location: Chapter 2, Section 2.4.3**

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**Submitter:** CropLife America (CLA)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Pg 19: "Risk Assessment Guidance for Superfund Volume..." The citation is not complete; this should be labeled as Volume I.

**EPA Response:** Text revised.

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### **Location: Chapter 2, Section 2.5**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** Page 22 (top): EPA mentions exposure assessment models used by the EU for REACH, but there is no mention of the models used by or developed by other national authorities or international agencies mentioned, e.g., Canada, OECD, etc.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** Page 23: Although much more discussion is needed on emerging exposure assessment approaches, at a minimum the discussion on page 23 should mention EPA's Exposure Toolbox (EPA-Expo-Box) and ExpoCast initiatives.

**EPA Response:** Text revised.

**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Data

**Comment Type:** Public

**Comment:** p. 21: In the section on occupational exposure guidance, consider citing the exposure reconstruction review paper by Sahmel et al. 2010.

**EPA Response:** Text revised.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Emerging Issues

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Emerging Issues

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Emerging Issues  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

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**Location: Chapter 2, Sections 2.4.1, 2.4.2 and 2.4.3**

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**Submitter:** U.S. Department of Defense (DoD)  
**Topic:** Editorial  
**Comment Type:** Public  
**Comment:** We do not see the value of presenting these overly simplistic equations for inhalation, ingestion and dermal exposure. Additionally, it seems odd to cite the previous version of the Exposure Guidelines for those equations, as this version of the Guidelines will supersede them.  
Recommend deleting the simplistic equations. It would seem more accurate and to the point to simply discuss that exposure is a function of concentration and rate of exposures.  
**EPA Response:** Text revised.

## **Chapter 3. Planning and Scoping and Problem Formulation for Exposure Assessments**

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**Location: Chapter 3**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT  
**Topic:** Planning and Scoping and Problem Formulation  
**Comment Type:** Peer Review  
**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** 1. Occupational exposure: EPA makes clear on page 2 that the Guidelines’ principal focus is on human exposure to chemicals in “non-occupational” scenarios. There are several instances in the document, however, where occupational exposures are discussed (e.g., Page 20, Box 2-1; Page 21; Page 31; Page 34; and Page 70, Table 5-2). EPA should review the document for these discussions and assess their appropriateness since this isn’t the focus of this document. Discussion of occupational exposures could create the perception that these are the most important occupational exposure assessment publications or concepts.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** 4. Is this Science Based Guidance or Potential Regulation? The draft Guidelines emphasize what science concepts to “consider” in conducting human exposure assessments and generally steer clear of mandates. Further, EPA makes clear (on page 2) that these Guidelines are not detailed instructions designed to “supplant” specific exposure guidance in use by EPA programs.

Yet on page 24, the Guidelines suggest that a risk assessment that is completed as part of a “regulatory action” could have various “legal considerations.” The document then lists five examples of statutes or regulatory programs whose “legal considerations could influence specific aspects of the assessment.” This language could be construed as suggesting that these Guidelines could, in fact, be imposed as requirements within the context of regulations. EPA program offices should be asked to comment on the potential impact and burden of these Guidelines on their programs, despite the page 2 disclaimer. EPA should also provide specific examples where legal considerations would supersede the Guidelines.

**EPA Response:** Text not revised; this is a guidelines document and places no mandates or requirements on either the agency or stakeholders as stated in the Preface, Executive Summary and Chapter 1.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; EPA conducts a variety of different levels of assessments under different authorities. Chapter 3 discusses the importance of coordinating with EPA staff to ensure the assessment meets programmatic needs.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Planning and Scoping and Problem Formulation

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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 exposures through drinking water systems.

**EPA Response:** Text revised.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because Section 3.1.2 refers the reader to Chapter 4 for consideration of lifestage, susceptibility and environmental justice.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because information on cumulative and aggregate exposure is mentioned in Sections 3.1.2 and 3.1.1, respectively.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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).

**EPA Response:** Text revised.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because references to community involvement (Section 3.1.3) and EPA’s peer review program (Section 3.1.4) are addressed in the document.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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 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-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.

**EPA Response:** Figure 3-1 moved.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Title not revised; communication is a component of planning and scoping and problem formulation, as described in the chapter.

---

**Location: Chapter 3, Page 25, Figure 3-1**

---

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** Item 3.4 “Communication Strategy” is very important and should have more weight and not just be an afterthought.  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 26, bullets**

---

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Should add: “ensuring that the exposures being assessed are relevant and important to the affected communities”  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 26, Figure 3-2**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Planning and Scoping and Problem Formulation  
**Comment Type:** Peer Review  
**Comment:** What does an arrow represent: flow of information through the process, or influence of one element upon another?  
**EPA Response:** Figure not revised as the arrows indicate the flow of information through the process and the influence of one element upon another.

---

**Location: Chapter 3, Page 27, 3rd paragraph in Section 3.1.1, line 1-2**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 27, last paragraph**

---

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Planning and Scoping and Problem Formulation  
**Comment Type:** Peer Review  
**Comment:** Project team needs to have representatives of the affected communities  
**EPA Response:** Text not revised as Section 3.1.3 details the role of the community in the process.

---

**Location: Chapter 3, Page 27, Section 3.1.1, 1st paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Good opening paragraph. I suggest moving the short and succinct final sentence to the beginning of the paragraph.  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 27, Section 3.1.1, 2nd paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Last sentence: I suggest changing text to read: ...fate and transport properties, and routes of exposure;  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 28, 2nd paragraph, 1st line**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** I suggest changing need to be to read should be.  
**EPA Response:** Text not revised because the emphasis is on considerations necessary to develop an assessment.

---

**Location: Chapter 3, Page 28, last line**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** “are required.” When done by whom? This gets to the question of who the intended audience is for this document.

**EPA Response:** Text not revised because aggregate exposure is required when conducting exposure assessments under some statutes. As noted in the Preface of this Guidelines, the primary users of this document are EPA staff.

---

**Location: Chapter 3, Page 29, 1st Paragraph, line 4**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 29, Section 3.1.2**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Suggested rewording: “It is essential that exposure assessors be cognizant of these overarching themes so that...”

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Aggregate and Cumulative Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because this section, as written, is consistent with the intent of the comment.

---

**Location: Chapter 3, Page 30, bottom bullets**

---

**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Planning and Scoping and Problem Formulation  
**Comment Type:** Peer Review  
**Comment:** Where do stakeholders figure in this?  
**EPA Response:** Text not revised because the first bullet addresses stakeholder involvement (e.g., Who might be affected by the exposure/risk assessment?).

---

**Location: Chapter 3, Page 30, first paragraph**

---

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Planning and Scoping and Problem Formulation  
**Comment Type:** Peer Review  
**Comment:** Open and transparent dialogue with the community is necessary to make sure that the exposure pathways are being appropriately characterized for the affected community  
**EPA Response:** Text not revised because Chapters 3, 7 and 9 address stakeholder involvement. Community is included as a stakeholder.

---

**Location: Chapter 3, Page 31, 1st paragraph in Section 3.1.4**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 31, 2nd paragraph**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Planning and Scoping and Problem Formulation  
**Comment Type:** Peer Review  
**Comment:** 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 afterthought.  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 32, 2nd paragraph, line 4**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Add “by external experts” after “”...will be peer-reviewed...”  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 33, 3rd paragraph, line 1**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Change “population” to “population(s)”  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 33, last paragraph, last line**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “into” can be deleted and the line changed to “occupation), lifestages...” to make the grammar parallel.  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 33, Section 3.2**

---

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Planning and Scoping and Problem Formulation  
**Comment Type:** Peer Review  
**Comment:** Problem formulation needs to address the “risk perceptions” of the affected community, otherwise how do you know if you will answer their questions?  
**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 33, Section 3.2, 1st paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** There is a reference to Microbial RA guidelines, but Chapter 1 states that this is outside the scope of the document.

**EPA Response:** Text not revised as the microbial risk assessment guideline reference provides an additional reference as an example.

---

**Location: Chapter 3, Page 33, Section 3.2.1, 1st line**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Suggest changing An important aspect to One important aspect.

**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 33, Section 3.2.1, 1st paragraph, 2nd sentence**

---

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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]

**EPA Response:** Text not revised because a specific recommendation for revision was not provided.

---

**Location: Chapter 3, Page 34, 1st line**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “assessments need to... understand...” An exposure assessment doesn’t understand anything; I suggest changing either the subject or the verb in this sentence.

**EPA Response:** Text revised.

---

**Location: Chapter 3, Page 34, 1st paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Planning and Scoping and Problem Formulation



**Comment Type:** Peer Review

**Comment:** Why only assess exposure situations that affect the most susceptible population?

**EPA Response:** Text not revised because Section 3.2.1 provides a range of approaches for assessing exposure.

  

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the text provides content regarding the role of a toxicologist in the exposure assessment.

  

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** Focus on first trimester and 1-18 months as these are the times most likely to affect outcomes for a lifetime

**EPA Response:** Text not revised because an in-depth discussion of lifestage is found in Chapter 4.

---

**Location: Chapter 3, Page 34, 3rd paragraph, line 8**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Change "assess" to "assessing"

**EPA Response:** Text revised.

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**Location: Chapter 3, Page 35, 6th bullet**

---

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text not revised because this is an exposure document.

---

**Location: Chapter 3, Page 37, Section 3.3.2**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** Are “environmental scenarios” and “exposure scenarios” the same thing?  
Because environmental scenarios are not discussed anywhere else.

**EPA Response:** Text revised. The term was changed to “exposure scenarios.”

---

**Location: Chapter 3, Page 37, Table 3-1**

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**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised. “Site assessment was retained under “Populations at Risk.” A site assessment looks at who is exposed, their activities and the exposure scenario. Typically, the assessment considers what properties are impacted, population/lifestage exposed and their activities. Overall, it links the contamination with the potentially impacted population. Accordingly, the population is retained in the “population” column.

---

**Location: Chapter 3, Page 38, last line**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text not revised because the Preface to the document identifies the audience stating: “This *Guideline for Human Exposure Assessment* is intended principally for exposure and risk assessors in the Agency and consultants, contractors or others who perform this type of work under Agency contract or sponsorship. It also is intended for academics, industry staff and others who perform this type of work in accordance with EPA policies and procedures. EPA risk managers/decision makers also need to be familiar with this document because it describes approaches, defines terminology and summarizes methods exposure and risk assessors use to support regulatory decisions.”

---

**Location: Chapter 3, Pages 36-37, Section 3.3.1**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** Any advice for using pre-existing data (like published research, etc.) when you don’t have control over the study design?

**EPA Response:** Text not revised because a discussion of Agency guidance on the use of existing data is provided in Section 5.3.2.

---

**Location: Chapter 3, Section 3.1**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because Section 3.1.1 identifies the importance of “dialogue among the project team to define the question at hand or the hypothesis the assessment seeks to address.”

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**Location: Chapter 3, Section 3.1.1**

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**Submitter:** CropLife America (CLA)

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Public

**Comment:** \*\*Pg 28: “When an element of risk is likely to be important but no valid data are available, an exposure assessor needs to highlight this deficiency or use judgment or default values to approximate the missing data.”

What is the recommended approach to obtaining valid data? Such guidance should be provided here.

**EPA Response:** Text not revised because Chapter 5 provides a discussion of data quality procedures with references.

---

**Location: Chapter 3, Section 3.1.2**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Aggregate and Cumulative Exposure Assessment

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because development of relative source contributions is specific to the Safe Drinking Water Act and associated guidance. Determinations of the application of relative source contributions is a program decision and beyond the scope of this document.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to better balance the discussion of topics. Sustainability is not the focus of this Guidelines and therefore is not covered in depth.

---

**Location: Chapter 3, Section 3.1.4**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** 2. Page 32, 2nd paragraph: ACC suggests changing "other agents with controversial methodology" to "other agents with complex methodology."

**EPA Response:** Text revised.

---

**Location: Chapter 3, Section 3.2.1**

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<b>Submitter:</b>	CropLife America (CLA)
<b>Topic:</b>	Planning and Scoping and Problem Formulation
<b>Comment Type:</b>	Public
<b>Comment:</b>	<p>Pg 33: “Population-based approaches commonly are used when information on the broader context of exposures is needed. In contrast to scenario-based approaches, a population-based approach frequently incorporates probabilistic methods with an objective to better estimate inter-individual variability in exposures or dose.”</p> <p>It is not clear under which kinds of situations EPA would not be interested in considering inter-individual variability. This should be clarified. Should inter-individual variability not be considered, would not uncertainty be created in the assessment outcomes.</p>
<b>EPA Response:</b>	Text not revised because the definition of population-based assessments concentrates on one population and high-end exposures are used in the assessment to avoid underestimating risks.

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**Location: Chapter 3, Section 3.2.2**

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<b>Submitter:</b>	Rebecca T. Parkin, Ph.D., MPH
<b>Topic:</b>	Planning and Scoping and Problem Formulation
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	The conceptual model shown in Chapter 5 (Figure 5-1) or a similar figure would be a valuable addition to Section 3.2.2.
<b>EPA Response:</b>	Text revised, including addition of a figure.

---

**Location: Chapter 3, Section 3.3.1**

---

<b>Submitter:</b>	American Chemistry Council (ACC)
<b>Topic:</b>	Planning and Scoping and Problem Formulation
<b>Comment Type:</b>	Public
<b>Comment:</b>	<p>3. Table 3-1: This table seems incomplete. ACC suggests adding at least “Product use” under sources, and something about environmental characteristics including micro-environments. Also the heading “exposure pathways” discusses land use and climate but it is unclear how those are exposure pathways. ACC recommends that this table be redesigned and expanded.</p>
<b>EPA Response:</b>	Text revised.

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**Location: Chapter 3, Section 3.4**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

## **Chapter 4. Consideration of Lifestages, Vulnerable Groups and Populations of Concern in Exposure Assessments**

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**Location: Chapter 4**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text not revised because this is an example of the use of the Atkinson index for reducing exposures to some agents and reducing disparity between populations. The narrative is intended to indicate the importance of data quantity and quality. The reference regarding migrant farm workers indicates that a national study does not necessarily require information across a broad geographic area but can involve populations that move across locations.

**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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 use them based on the information provided.

**EPA Response:** Text not revised because the text describes EPA’s current efforts on lifestyles, vulnerable groups and populations of concern in exposure assessment.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Chapter 4’s discussion of the consideration of life stages, vulnerable groups and populations of concern in exposure assessments is an important update to the 1992 Guidelines. It takes a very broad-brush approach to discussing these important issues, however, offering little specific guidance and examples for practitioners. The Chapter’s wide ranging discussion of environmental justice could lead to significant confusion, misunderstanding and errors regarding how exposure

assessors should approach these issues. For these reasons, EPA should pay close attention to this chapter in its next draft. Peer reviewers should examine assumptions and seek to clarify concepts and terms to ensure that Chapter 4 focuses on the actual science and practice of exposure assessment involving life stages, vulnerable groups and populations of concern.

**EPA Response:** Text revised.

**Submitter:** American Petroleum Institute (API)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Environmental Justice. In Chapter 4, EPA addresses a range of socioeconomic and other attributes that can affect exposure assessments. The Chapter includes an important discussion of environmental justice issues. We are concerned, however, that in this discussion EPA has incorrectly made a causal link between increased exposure potential and increased sensitivity to a stressor. While increased sensitivity may be related to increased exposure, it is false to assume that this is always the case. If in a specific case sensitivity to a stressor is known to be related to increased exposure, this should be addressed in the dose-response characterization phase of the risk assessment. In cases in which socioeconomic or racial factors may result in disproportionate exposure, this is appropriately addressed in the exposure data and then factored into the risk assessment phase. The ACC has provided additional comments on this topic which we endorse.

**EPA Response:** Text not revised because the document incorporates considerations of lifestages, vulnerable groups and populations of concern in exposure assessments consistent with how the Agency addresses exposure and risk assessments for this complex topic. Relevant examples and resources for additional information are provided.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the relationship between exposure and dose is discussed in Chapter 2.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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 Lifestyles, 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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  $\bar{x}$  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 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the document includes several references to statutes, executive orders and other policy statements that identify populations and lifestages of concern. A supplemental discussion of the effects of an immature immune system or depleted recuperative abilities due to age or impaired resistance due to stress from malnutrition or other non-chemical stressor(s) is beyond the scope of the document.

**Submitter:** The Teratology Society

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** In Chapter 4, there is a brief mention of lifestages, including pregnancy and lactation. Although eating habits and changes to nutritional needs are cited, there is no mention of the physiological parameters that change due to pregnancy, and which also vary throughout pregnancy as the demands of the conceptus change.

**EPA Response:** Text not revised because the example highlights how potential exposures might change at various lifestages.

---

**Location: Chapter 4, Page 39, 1st paragraph, line 11**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review  
**Comment:** A third paragraph could begin with “The public...”  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 39, 1st paragraph, line 6**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** A second paragraph could begin with “Incorporating...”  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 39, 1st paragraph, lines 14-16**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “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.  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 39, 2nd paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** “assessments involving potentially vulnerable populations.” Don’t they all?  
**EPA Response:** Text not revised because Section 4.4 includes a range of considerations used to identify vulnerable populations.

---

**Location: Chapter 4, Page 40, 2nd paragraph, line 3**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Aggregate and Cumulative Exposure Assessment  
**Comment Type:** Peer Review

**Comment:** Why just “especially aggregate exposure”? Why not cumulative, as well?

**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 40, Box 4-1**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Should add Executive Order 12898 Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

**EPA Response:** Text not revised because Executive Order 12898 is the first bullet.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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) Identify and address 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 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.

**EPA Response:** Text not revised because the purpose of Box 4-1 is to highlight the executive orders and not reproduce them in their entirety.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Revise title to read “Provisions of Presidential Executive Orders.” No Agency policies are included here.

**EPA Response:** Text revised so that the title of Box 4-1 reads “Provisions of Presidential Executive Orders.”

---

**Location: Chapter 4, Page 40, Section 4.2, 1st paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “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...”

**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 41, Box 4-2**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** Is the 2008 Child-Specific Exposure Factors Handbook not included because the 2011 EFH incorporates all of it? (Same comment for Box 4-3)

**EPA Response:** Text not revised because EPA’s *Exposure Factors Handbook: 2011 Edition* supersedes all other versions, including the *Child-Specific Exposure Factors Handbook*.

---

**Location: Chapter 4, Page 42, bullets**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because socioeconomic status is listed in the discussion of differential exposure.

---

**Location: Chapter 4, Page 42, Figure 4-1**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Figure clarified.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text not revised because the figure captures the thought provided by the reviewer.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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?”

**EPA Response:** Text in figure clarified.

---

**Location: Chapter 4, Page 43, after bullets**

---

**Submitter:** Christopher W. Greene, M.S.



**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** The first sentence of this paragraph is repeated from page 40. I suggested an edit there—see above.  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 43, last bullet**

---

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Add chronic stress and exposure to violence  
**EPA Response:** Text not revised because three examples are provided in the text.

---

**Location: Chapter 4, Page 43, line 2**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Is there a standard sort order for citations? This list is not oldest-to-newest or newest-to-oldest. (Are they all done alphabetically?)  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 43, Section 4.2, last paragraph, lines 1-3**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** From “Considering,” this repeats the first paragraph of 4.2.  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 43, top**

---

**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because assessments for consumption of fish consider various age groups (children, adolescents, adults). Based on bioaccumulation of contaminants in fish, consumption is generally a major risk driver for all age groups.

---

**Location: Chapter 4, Page 44, 1st paragraph, lines 13-15**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** "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.

**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 44, first full paragraph, line 13**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** From "During" could be a new paragraph.

**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 44, last paragraph**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** Newborns, e.g., less than 1-3 months old, do not eat apples or even apple sauce.

**EPA Response:** Text not revised because the text is correct as written, as verified from Table B-1a in the citation.

---

**Location: Chapter 4, Page 44, Section 4.3.2, 1st paragraph.**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** In the quotation of EO 13045, I suggest changing the colon to an ellipsis (...)  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 45, 2nd paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** 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.”  
**EPA Response:** Text not revised because included citations support the text.

---

**Location: Chapter 4, Page 45, line 3**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** “the relationships between maternal and fetal exposures...” You may want to note that all of this is highly chemical-specific.  
**EPA Response:** Text not revised because included citations support the text.

---

**Location: Chapter 4, Page 45, Table 4-1**

---

**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised because childhood age groups are consistent with U.S. EPA (2005c).

---

**Location: Chapter 4, Page 46, Box 4-3**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** No mention of the Child-Specific EFH? Or was this superseded by the 2011 EFH?  
**EPA Response:** Text not revised because the *Exposure Factors Handbook: 2011 Edition* supersedes all other versions and includes data on child-specific exposures.

---

**Location: Chapter 4, Page 46, Figure 4-2**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** 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?  
**EPA Response:** Text not revised because details are provided in primary citation.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** From page 43, childhood includes the prenatal period. Any insight to add to this chart?  
**EPA Response:** Figure 4-2 not revised because it is focused on children’s activities. Although the prenatal period might be part of childhood, there are no child-specific activities to capture.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Figure revised.

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Figure revised.

---

**Location: Chapter 4, Page 46, Figure 4-2, school line**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** Why aren’t ages 3-5 indicated as “initiating activity?” Many children are in school-like settings during this “window.”  
**EPA Response:** Figure revised.

---

**Location: Chapter 4, Page 46, Table 4-2**

---

**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 47, bullets**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** 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?  
**EPA Response:** Text not revised because definitions are addressed in Section 4.3.1.

---

**Location: Chapter 4, Page 47, Section 4.3.3**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** Special considerations should also be considered for pregnant women and women of child bearing age

**EPA Response:** Text not revised because Section 4.3.2 addresses pregnant women and their potential exposures.

---

**Location: Chapter 4, Page 47, Section 4.3.4**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter.

---

**Location: Chapter 4, Page 47, Section 4.3.4, lines 9-12**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 48, 2nd paragraph**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** The number 1,969,167 seems quite precise given the births and deaths of any population of this size during a one-year period.

**EPA Response:** Text not revised because this value is listed in the citation.

---

**Location: Chapter 4, Page 48, Table 4-2**

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<b>Submitter:</b>	P. Barry Ryan, Ph.D.
<b>Topic:</b>	Lifestages, Vulnerable Groups and Populations of Concern
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	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.
<b>EPA Response:</b>	Table not revised because the citation to the externally peer-reviewed <i>Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens</i> is provided for more information.
<b>Submitter:</b>	Paloma Beamer, Ph.D.
<b>Topic:</b>	Lifestages, Vulnerable Groups and Populations of Concern
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	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.
<b>EPA Response:</b>	Table not revised because additional information is provided in the citations.

---

**Location: Chapter 4, Page 48, Table 4-2, last column header**

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<b>Submitter:</b>	Michael A. Jayjock, Ph.D., CIH
<b>Topic:</b>	Editorial
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	[Cancer] Potency Adjustment (U.S. EPA 2005h)
<b>EPA Response:</b>	Text revised.

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**Location: Chapter 4, Page 49, 2nd bullet**

---

<b>Submitter:</b>	Christopher W. Greene, M.S.
<b>Topic:</b>	Editorial
<b>Comment Type:</b>	Peer Review

**Comment:** Re-word the first sentence. How are data “gathered potentially?”

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** What are “the issues of informed consent?” Please elaborate.

**EPA Response:** Text not revised because the reader is referred to Section 7.2.10 for additional information.

---

**Location: Chapter 4, Page 49, 3rd paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “The percentage subsistence and frequency...” Percentage of what?  
Frequency of what?

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Suggest changing fish or other game to fish and game.

**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 49, after box**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** Clarify what is meant by advisories

**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 49, Box 4-4**

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**Submitter:** P. Barry Ryan, Ph.D.



**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** There are either inconstancies or unclear parallels in wording in this Box  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 49, last bullet**

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**Submitter:** Alan H. Stern, Dr. P.H., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Move “potentially” to after “are.”  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 49, paragraph below box**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** “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.  
**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** Some citations for the statements in this paragraph would help direct the reader to more details.  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 50, 2nd bullet**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Science is NOT an exclusively western construct. I recommend rewording this.  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 50, 2nd to last paragraph**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “EPA mandates...” For whom?  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 50, last bullet**

---

**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** Are these based on anecdotal observations or evidence based?  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 51, 2nd to last paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** “...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.  
**EPA Response:** Text not revised; no revision necessary because assessments typically are designed to address exposures at a specific location. These concepts can be addressed in planning and scoping and problem formulation during which decisions regarding the scope and extent of the assessment are defined.

---

**Location: Chapter 4, Page 52, Section 4.3.6**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** Perhaps include immigrants and refugees in this discussion too  
**EPA Response:** Text not revised because the purpose of Section 4.3.6 is to bring awareness to unique exposure considerations for diverse racial and ethnic populations. Immigrants and refugees fall into this category.

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**Location: Chapter 4, Page 52, Section 4.3.6, 2nd paragraph**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** Last sentence. What did they find?  
**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 53, 1st line**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Peer Review  
**Comment:** Anything to report on differences in consumption between generations, i.e., first-generation immigrants and their children?  
**EPA Response:** Text not revised because published studies were not identified.

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**Location: Chapter 4, Page 54, middle**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “Reduced levels” implies they used to be more highly regulated. Should this be changed to “lower levels?”  
**EPA Response:** Text revised.

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**Location: Chapter 4, Page 55, Box 4-6**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Text says “X is\_\_\_.” Something seems to be missing.  
**EPA Response:** Text revised.

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**Location: Chapter 4, Page 56, Box 4-6**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The version of the document I received had a missing term in “X=.” Others commented on this in the context of completing the text

**EPA Response:** Text revised.

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**Location: Chapter 4, Page 56, Box 4-6, 1st line after equation**

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**Submitter:** Alan H. Stern, Dr. P.H., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Something is missing (underscore).

**EPA Response:** Text revised.

---

**Location: Chapter 4, Page 57, 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** How can this information be applied within the document’s framework of exposure assessment? Based on Chapter 1, this may be outside the scope, but if possible, something should be said about application.

**EPA Response:** Text not revised because social stressors are outside the scope of the document (see Section 1.2 Purpose and Scope). For completeness, a mention of social stressors is included in Chapter 4.

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**Location: Chapter 4, Page 57, last paragraph**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the text provides links and references to various GIS tools where detailed information can be obtained.

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**Location: Chapter 4, Page 57, last paragraph, lines 15-16**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** EPA's C-FERST says the tool prioritizes issues, not exposures. This sentence should be modified.

**EPA Response:** Text revised.

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**Location: Chapter 4, Page 58, Section 4.4.1**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** "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.

**EPA Response:** Text not revised because this is a risk management decision outside the scope of this document.

---

**Location: Chapter 4, Page 59, Section 4.4.5, line 2**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** "pollution exposures." Any reason not to say "chemical exposures?"

**EPA Response:** Text revised.

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**Location: Chapter 4, Page 60, 3rd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** Is there a reference for the pesticide poisoning figure?

**EPA Response:** Text revised.

---

**Location: Chapter 4, Section 4.3.2**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** 3. Page 46 Figure 4-2 could benefit from clarification that it represents a heat map, or alternatively all specific gradations in color should be defined in the legend.

**EPA Response:** Text revised to include the gradation of color found in Figure 4-2.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** 5. Section 4.3.2 states that “[c]hildren also have higher excretion and metabolic rates per unit of body than adults.” It should be noted that rates can actually be lower in young infants. It is recommended, therefore, that the statement be more comprehensive.

**EPA Response:** Text not revised because the paragraph discusses children and provides supporting references. The infant age ranges are not included in the discussion.

**Submitter:** Consumer Specialty Products Association (CSPA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** CSPA notes that the discussion in Section 4.3.2 that “Children also have higher excretion and metabolic rates per unit of body than adults” but recommends that other sub-populations can have much lower metabolic rates and recommended that the statement be more comprehensive.

**EPA Response:** Text revised.

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**Location: Chapter 4, Section 4.3.3**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** 7. Page 47. ACC suggests deleting “pesticide exposures from playing golf on treated turf are relatively age independent.” This is not necessarily true as in the context of the other example provided, there is a bias in the age of people who golf. In fact, children are often not allowed on golf courses, so that is not a lifestage of typical concern.

**EPA Response:** Text revised.

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**Location: Chapter 4, Section 4.3.4**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** 6. Page 47-48. Additional content should be provided on Table 4-1 regarding the potency adjustment for each age group. How have these potency adjustments been derived and are there any limitations or application boundaries to consider during application? Also, it should be explicitly stated that if an exposure estimate already adjusts for differences in age groups that account for any age related potency differences care should be exercised before applying another adjustment factor for potency.

**EPA Response:** Text revised.

**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** \*\*Pg 47: “For example, when assessing risks of carcinogens with a mutagenic mode of action, different toxic potency adjustments are made for exposure of children less than 2 years of age and between 2 and less than 16 years old (U.S. EPA 2005h).”

It is not clear that this approach to cancer risk assessment is well-supported by the scientific literature cited in the EPA 2005 document, and/or whether any literature published since 2005 (the year of publication of the EPA document) supports this statement. If that is not the case, this example should not be used and the statement removed.

**EPA Response:** Text revised.

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**Location: Chapter 4, Section 4.3.6**

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**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Pg 53, section 4.3.6, Other Racial and Ethnic Populations: No guidance is provided as to how exposure assessors should incorporate information on these populations similar to guidance offered for other populations in this chapter.

Resources and recommendations should be added.

**EPA Response:** Text not revised because citations are included in this section and examples show how cultural practices and traditions need to be considered.

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**Location: Chapter 4, Section 4.3.7**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** 8. Page 53. ACC suggests revising to “Socioeconomic Factors to Include Consider in Exposure Assessment”

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** 9. Page 54-56. Different terms have been used to refer to the parameter  $\epsilon$  in the Atkinson index calculation. It is referred to as a sensitivity parameter on page 54 but on page 56 it is referred to as the degree of weight in the equation. These should be consistent.

**EPA Response:** Text not revised because Atkinson index is defined in Box 4-6.

**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Pg 57, Social Stressors: The Guidelines offer no information on how to incorporate stress into an exposure assessment. How would social stressors be characterized, measured or monitored? This is not clear from these guidelines.

**EPA Response:** Text not revised because social stressors are discussed in Section 4.3.4 with references.

**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Pg 54-55: From the text in the section on Socioeconomic Position and Class, it is unclear how the exposure assessor is supposed to use income inequality in designing an exposure assessment.

Should income inequality considerations be a part of every assessment? If not, which ones?

How would this aspect of a population be included in exposure assessment plan development?

**EPA Response:** Text not revised because this level of detail is beyond the scope of this document.

**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)



**Topic:** Editorial  
**Comment Type:** Public  
**Comment:** p. 56: text appears to be missing in Box 4-6 at “X is\_\_\_\_\_”  
**EPA Response:** Text revised.

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**Location: Chapter 4, Section 4.4**

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**Submitter:** American Chemistry Council (ACC)  
**Topic:** Editorial  
**Comment Type:** Public  
**Comment:** 11. Page 58. More than two methods have been discussed in section 4.4, but the overview paragraph in the beginning of the section only indicates two approaches are available to identify vulnerable groups.  
**EPA Response:** Text revised.

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**Location: Chapter 4, Section 4.4.1**

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**Submitter:** CropLife America (CLA)  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Public  
**Comment:** Pg 58: “In response to recommendations from an EPA symposium on environmental justice, the Agency commissioned a systematic review of proximity analysis and GIS methods (Maantay et al. 2010).”  
  
Maantay et al. (2010) is a slide presentation that can be found in EPA’s archived documents (<http://archive.epa.gov/ncer/ej/web/pdf/maantay.pdf>). Among their conclusions, they note: “...Given that racial/ethnic minorities and/or lower-income populations are more likely to live near such environmental hazards, and research has indicated that this residential characteristic might be associated with adverse health outcomes, it is highly likely that there is a disproportionate impact of this exposure on the health of minorities and lower income populations,  
  
However, few studies have examined whether such exposure are more or less likely to increase risk for adverse health outcomes among minority and lower income populations.” Maantay et al. (2010) offer many research recommendations - including some related specifically to exposure assessment – that will require attention. The results and issues raised by Maantay et al. (2010) should be included in the Guidelines.  
  
**EPA Response:** Text revised.

**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** \*\*Pg 58: “those using a ZIP code or larger area of analysis tend to find that income is a greater risk factor than race/ethnicity for exposure to environmental burdens, whereas studies using block groups or census tracts have tended to find that race/ethnicity is a greater risk factor than income for exposure.”

Much guidance needs to be provided given the contradictions and also the general lack of guidance on how to use tools.

How should the exposure assessor interpret this contradiction?

How does this relate to the information on pg 57, which describes geographic tools that provide information on income and environmental exposure based on geographic location?

What is the intent of this part of the Guidelines?

What are the strengths and weaknesses of these tools and are they ready for use?

What degree of confidence should assessors have in these tools?

**EPA Response:** Text not revised because references to the GIS tools include information on their application and use.

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**Location: Chapter 4, Section 4.4.3**

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**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** \*\*Pg 58: “The neighborhood pollutant or pollution source levels then are compared to national or regional means.”

Why compare neighborhood levels to regional means? Why not compare distributions?

The Guidelines should be specific about the required commonalities in the databases being compared. For example, how similar do the data collection time frames need to be? How representative do the regional/national data need to be (and how is representativeness defined)? How similar do analytical techniques need to be for comparisons to be valid?

Do regional/national data from hotspots need to be excluded? As an aside, for certain commonly measured chemicals such as metals, naturally occurring background concentrations will vary according to geographic location and comparison of regional and national data must consider this issue (Shacklette and Boerngen 1984).

**EPA Response:** Text not revised because the suggested level of detail is beyond the scope of this document.

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**Location: Chapter 4, Section 4.4.5**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** 12. Page 59. The association identified (e.g., through regression analysis) does not mean causal relationship. The last sentence in section 4.4.5 should be revised to “any additional evidence, however, is needed to assess causation” instead of “might be needed to assess causation.”

**EPA Response:** Text revised.

**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** \*\*Pg 59: “These methods can be valuable in screening for potential associations between multiple risk factors and differences in health between racial and other groups. Additional evidence, however, might be needed to assess causation [emphasis added].”

This is an extremely important and relevant point to be made. Causation is quite difficult to demonstrate; further, it is outside the scope of Guidelines on exposure assessment.

**EPA Response:** Text not revised because the concept is supported in the text.

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**Location: Chapter 4, Section 4.4.6**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** 13. Page 60. When discussing the NATA data, it is important to note the caveats and limitations of the program. We suggest using this link which helps to explain how the data should and should not be used: [http://www.epa.gov/national\\_air-toxics-assessment/nata-frequent-questions](http://www.epa.gov/national_air-toxics-assessment/nata-frequent-questions) (see questions 3 and 4).

**EPA Response:** Text not revised because the section provides only an overview of national assessment tools. User application/implementation caveats are available via NATA’s website (which is provided).

**Submitter:** American Chemistry Council (ACC)  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Public  
**Comment:** 14. Page 60: Community level exposure assessment is a topic of interest to EPA. Not mentioned in these Guidelines, however, are the more updated software programs and databases that evolved from EPA's OPPT between 2002 and 2008.  
**EPA Response:** Text not revised because the primary database is the Toxics Release Inventory, which is mentioned in Sections 4.4.1 and 4.4.6.

**Submitter:** CropLife America (CLA)  
**Topic:** Lifestages, Vulnerable Groups and Populations of Concern  
**Comment Type:** Public  
**Comment:** \*\*Pg 59: "At the national level, screening for differential exposure can use the large, comprehensive databases developed by national organizations, such as EPA, the U.S. Bureau of the Census and the Centers for Disease Control and Prevention (CDC), on pollutant concentrations in environmental media (e.g., air, water) and the locations of pollution sources. For example, the screening study might combine data on segregation and income inequality, metropolitan air quality indices, modeled air toxics concentrations and data from the Toxics Release Inventory. One example of a national-level assessment is EPA's National-Scale Air Toxics Assessment (NATA; <http://epa.gov/airtoxics/natamain/>), an ongoing comprehensive evaluation of air toxics in the United States."  
These kinds of databases require special attention and the Guidelines should alert the reader to the various limitations. For example, the description of NATA (which is now at a different URL from the one given in the Guidelines) does not include its many limitations.

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EPA's NATA site includes the following statement: "EPA suggests that the results of this assessment be used cautiously, as the overall quality and uncertainties of the assessment will vary from location to location as well as from pollutant to pollutant. In many cases more localized assessments, including monitoring and modeling, may be needed to better characterize local-level risk."

Further, EPA lists the many limitations of the database as follows:

- The results apply to geographic areas, not specific locations.
- The results do not include impacts from sources in neighboring countries (i.e., Canada or Mexico).
- The results apply to groups, not to specific individuals.

- The results are restricted to the year of the analysis since emissions for that year were used.
- The results do not reflect exposures and risk from all compounds.
- The results do not reflect all pathways of exposure.
- The results reflect only compounds released into the outdoor air.
- The results do not fully reflect variation in background ambient air concentrations.
- The results might systematically underestimate ambient air concentration for some compounds.
- The results used default, or simplifying, assumptions where data were missing or of poor quality.
- The results may not accurately capture sources that have episodic emissions (e.g., prescribed burning or facilities with short-term deviations such as startups, shutdowns, malfunctions, and upsets).
- Estimates of risk are uncertain.

This kind of information is essential for exposure and risk assessors and should be included in the Guidelines.

**EPA Response:** Text not revised because, as the commenter points out, the limitations of any dataset are provided in the primary resources.

**Submitter:** CropLife America (CLA)

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** \*\*Pg 60: “Another example of a national-level assessment would be that associated with examining exposure of migrant agricultural workers to pesticides. This type of exposure is national in the sense that migrant workers are not only employed throughout the United States, but they also tend to move from one location to another during the year. According to CDC, doctors diagnose between 10,000 and 20,000 farm workers with pesticide poisonings each year. Workers can become exposed to toxic levels of pesticides during spills, direct spraying or pesticide drift. In addition, migrant farm workers might not be supplied the protective gear needed to protect their health or the equipment they do receive is defective. To help reduce risks to migrant farm workers associated with pesticide exposures, EPA has awarded grants to train migrant farm workers in southern New Jersey about steps they can take to protect their health on the job more effectively.”

While this kind of information is critical for worker health and safety, worker protection against poisonings appears to be outside the scope of these Guidelines which are not occupationally focused. Further, the Guidelines do not offer

guidance on how to incorporate occupationally related poisoning information into exposure assessments.

**EPA Response:** Text revised.

**Submitter:** CropLife America (CLA)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Pg 60, Local-Level (Community) Assessment: How does this section differ from Section 4.4.3 on Neighborhood Methods?

**EPA Response:** Text revised.

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**Location: Chapter 4, Sections 4.3.1 through 4.3.4**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** 4. ACC suggests that Section 4.3.1-4 should be re-organized by starting with a general discussion and then moving into discussion of specific lifestages. Specifically, Section 4.3.1 should present a general discussion of the importance of considering lifestages, rather than a discussion of children only. The child specific discussion could then take place in Section 4.3.2 that covers this lifestage in detail. Also, Section 4.3.3 currently gives the impression that it refers to older adults only; it should be expanded, especially the examples, if it is meant to be broader in scope. It may be useful to include additional lifestages (e.g. women during pregnancy).

**EPA Response:** Text not revised because the document includes the important information mentioned by the commenter.

## **Chapter 5. Data for Exposure Assessments**

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**Location: Chapter 5**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to provide additional information regarding biomonitoring. Table 5-1 updated to include information regarding dust as an exposure route. The recommendation to coordinate with the programs to establish analytical methods is emphasized in the text.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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 this document.

**EPA Response:** Text revised to identify types of data in Section 5.1. Table 5-6 updated to include additional links to information on food products from the USFDA and USDA.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:**

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.

**EPA Response:** Text revised and Tables 5-2 and 5-3 updated. Tables 5-1 and 5-3 updated to include exposures mentioned in comments.

Bulleted paragraph, “Were the data collected close to an exposure point of concern in space and time?” expanded consistent with the comment.

Table 5-3 expanded and updated consistent with comments.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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).

**EPA Response:** Text revised to update links to the EPA Modeling and Measurements webpage that provides information on EPA’s modeling efforts and contacts for further information on specific models. The webpage includes “Models at EPA” that lists some of the models and modeling programs at EPA.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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:

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.

**EPA Response:** Text revised to list three references regarding statistical approaches to address non-detects.

Text revised to update link to the Modeling and Measurement webpage. The text also directs the reader to Chapter 6 for additional information on modeling.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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 important 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.

**EPA Response:** Text revised to identify additional evaluations of low-quality data consistent with comment. HERO database identified as a resource.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to reduce redundancy.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

Section 5.4 does not consider how to determine when the available data and related knowledge are enough. Clearly, "enough" needs to be anchored in the context of the driving question/hypothesis of the assessment.

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.

**EPA Response:** Figure 5-1 moved to Chapter 3 and updated to include information on exposures associated with the conceptual site model. Table 5-2 text updated to emphasize the importance of identifying the study objective. Further discussion regarding timeframe included in section, Identifying Data Gaps and Data Needs.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the comment is a summary of the overall goals of the chapter.

---

**Location: Chapter 5, Page 102, Table 5-6**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Table 5-6 includes a link to the USGS Environmental Health webpage that includes links to USGS programs and contact information.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 2nd to last row: description of WQ Portal. You might add that the portal relies in part on STORET and USGS's NWIS database.

**EPA Response:** Text revised to include the STORET and USGS NWIS database information.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** In the “not exhaustive” note at the end of the table, you might add that many states have environmental databases as well.  
**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Table 5-6 revised to include information on the UCMR database.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** 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>  
**EPA Response:** Table 5-6 revised to include additional databases.

---

**Location: Chapter 5, Page 61, 1st paragraph**

---

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** What is meant by “health survey and study output”?  
**EPA Response:** Text revised to include example of a health survey, for example, NHANES.

---

**Location: Chapter 5, Page 61, 1st paragraph, 2nd sentence**

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**Submitter:** Michael A. Jayjock, Ph.D., CIH  
**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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].

**EPA Response:** Text revised to include model input parameters.

---

**Location: Chapter 5, Page 61, 2nd bullet**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Suggest writing acronym reference as “quality assurance/quality control (QA/QC)”

**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 61, last paragraph, line 7**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “potential future” sounds redundant. Wouldn’t “potential” suffice?

**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 62, Table 5-1**

---

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Table revised.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** Why include workers if this is non-occupational



**EPA Response:** Text not revised because references to information on workers are included in the table for completeness.

---

**Location: Chapter 5, Page 63, 1st set of bullets**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** Can this section address the use of geographical surrogate data, i.e., data gathered at another location with similar exposure concerns?  
**EPA Response:** Text not revised because discussing use of surrogate data is beyond the scope of the Guidelines.

---

**Location: Chapter 5, Page 63, 2nd paragraph**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** The focus of this paragraph would stand out better with a subheading: 5.1.1. Available Data  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 63, 2nd paragraph, line 6**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** Is EPA 1992b the most current “take” on this topic or has it been updated?  
**EPA Response:** Text revised to include additional guidance, for example, U.S. EPA (2005h).

---

**Location: Chapter 5, Page 63, 3rd bullet**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** These bullets (paragraph above) are good. The 3rd bullet: Good question, but the answer can be subjective.

**EPA Response:** Text not revised because the comment does not provide specific recommendations for revisions.

---

**Location: Chapter 5, Page 63, 3rd paragraph, line 2**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Should “need” be “could?”  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 63, 4th paragraph**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** A subheading (5.1.2. New Data) would help clearly distinguish this type of data from the discussion about existing data.  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 63, 4th paragraph, Question 1**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** I’d want to know about the nature/kind of data available as well as its quantity  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 63, 6th paragraph, Question 2**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** I’d want to know if the methods had been validated before being adopted  
**EPA Response:** Text revised to include question on validation.

---

**Location: Chapter 5, Page 63, last bullet**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Clarify uncertainty of what. The modeling outcome?  
**EPA Response:** Text revised to indicate uncertainty in data.

---

**Location: Chapter 5, Page 63, top of page**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised because the process needs to begin with defining data quality objectives to assess the usability of the data for the specific process.

---

**Location: Chapter 5, Page 68, 1st bullet**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** When is “peer involvement” to occur? This bullet is not clear about the timing.  
**EPA Response:** Text not revised because the text indicates peer involvement occurs throughout the process.

---

**Location: Chapter 5, Page 69, 4th paragraph.**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** 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

**EPA Response:** Text not revised because EPA's quality guidance outlines specific procedures for addressing reagents and blanks. Further details are provided in EPA's *Guidance for the Preparation of Standard Operating Procedures* (QA/G6), April 2007. The QA/G6 document is available at: [https://www.epa.gov/sites/production/files/2015-10/documents/chap1\\_1.pdf](https://www.epa.gov/sites/production/files/2015-10/documents/chap1_1.pdf).

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**Location: Chapter 5, Page 70, 1st bullet**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** The DL divided by the square root of two is also commonly used.

**EPA Response:** Text revised to include three additional guidance documents that address statistical evaluation of non-detects.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** Last sentence: is there a hard limit on the ratio of nondetects to total number of samples, below which substitution should never be used?

**EPA Response:** Text revised to include additional guidance documents that address statistical evaluation of non-detects.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** Should discuss effect of substitution on variance/standard deviation as well as mean. This is often forgotten.

**EPA Response:** Text revised to include three guidance documents on statistical analysis of data.

---

**Location: Chapter 5, Page 70, 1st paragraph, line 9**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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

**EPA Response:** Text not revised because this recommendation to coordinate with the program is highlighted throughout the document.

---

**Location: Chapter 5, Section 5.2.2**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** 6. Page 70. Additional methods for addressing non-detect values should be included. For simple substitution methods, frequently used substitutions also include  $DL/\sqrt{2}$  (Baccarelli et al., 2005)<sup>27</sup>. In addition to the three classes of techniques listed in the report, multiple imputation provides a useful strategy for handling datasets with non-detectable values. Instead of filling a single value for each missing value, multiple imputation replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute (Rubin, 1987)<sup>28</sup>. Then these multiple imputed datasets are analyzed by using standard procedures for complete data. Finally, the results from these impute datasets are combined for the inference (Yuan et al.)<sup>29</sup>.

Footnotes:

<sup>27</sup> Baccarelli, A., Pfeiffer, R., Consonni, D., Pesatori, A.C., Bonzini, M., Patterson Jr., D.G., Bertazzi, P.A., Landi, M.T. (2005), Handling of Dioxin Measurement Data in the Presence of Non-detectable Values: Overview of Available Methods and Their Application in the Seveso Chloracne Study.

<sup>28</sup> Rubin, D.B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, Inc.

<sup>29</sup> Yuan, Y.C. Multiple Imputation for Missing Data: Concepts and New Development (Version 9.0).

**EPA Response:** Text revised to include additional guidance documents that address statistical evaluation of non-detects.

**Submitter:** Virginia Department of Environmental Quality (DEQ)

**Topic:** Data

**Comment Type:** Public

**Comment:** Section 5.2.2.-page 71: Calculation of exposure point concentrations is driven by the requirements of regulatory programs and/or other guidelines. Some may require maximum values, specific media, upper bound of the mean, etc. Please include a discussion of how these requirements may impact the exposure assessment.

**EPA Response:** Text revised and references added.

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**Location: Chapter 5, Page 71, 3rd section**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** Is there any statistical criteria that should be used to determine if data sets can be combined?  
**EPA Response:** Text not revised because the included reference, U.S. EPA (2000), *Guidance for Data Quality Assessment*, contains detailed explanations of criteria to consider when combining data sets.

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**Location: Chapter 5, Page 71, 4th paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** The Dean methods are quite old and have been improved upon.  
**EPA Response:** Text not revised because the Dean method is listed in many textbooks on statistics and inclusion of the reference in this document is consistent with current statistical practice. Three references to guidance documents regarding evaluation of non-detects are also provided.

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**Location: Chapter 5, Page 71, line 3**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** I suggest not capitalizing the term open source.  
**EPA Response:** Text revised to delete discussion of the R software.

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**Location: Chapter 5, Page 72, 1st paragraph**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Data  
**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the document emphasizes the importance of coordinating with EPA programs to obtain current specific regulatory requirements.

---

**Location: Chapter 5, Page 72, Section 5.3.2**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:** “Biomarkers are...measures that can indicate exposure.” Is the biomarker a measure, or a thing that is measured?

**EPA Response:** Text not revised. In response to the question, biomarkers are measured. This is consistent with the definitions in Table 2-2 and Section 5.1.2.

---

**Location: Chapter 5, Page 73, Figure 5-3**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:** This Figure has been around for a while and I believe it has been “cleaned up” from this hand-drawn version.

**EPA Response:** Text not revised because it is the published figure in the referenced document.

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**Location: Chapter 5, Page 74**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to provide information regarding ExpoFirst, which is now available.

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**Location: Chapter 5, Page 75, Figure 5-4**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** This figure appeals to assume normality in the exposure estimate. Alternative strategies exist.  
**EPA Response:** Text not revised because this is an example.

---

**Location: Chapter 5, Page 76, 1st paragraph, lines 4-6**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** This quote is not in the resource cited. Identify the correct source.  
**EPA Response:** Text revised to indicate the quote is from ExpoFirst Glossary based on EPA's *Exposure Factors Handbook: 2011 Edition*.

---

**Location: Chapter 5, Page 76, Box 5-2**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** 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?  
**EPA Response:** Text not revised. The term MEI is defined under section 112 of the Clean Air Act Amendments of 1990.

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**Location: Chapter 5, Page 77, 2nd paragraph, line 2**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Add sentence reminding reader that "They may, or may not, be the same as those found in the Exposure Factors Handbook."  
**EPA Response:** Text revised to indicate that exposure factors might or might not be from EPA's *Exposure Factors Handbook: 2011 Edition*.



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**Location: Chapter 5, Page 77, Section 5.3.4, 1st paragraph, lines 8-10**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “needs to consider” seems too weak. Shouldn’t this be a “must” statement?  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 77, Section 5.4, 4th paragraph**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** “represent only some” begs the question as to how resources were chosen. If even one explicit criterion was used, then state it here.  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 78, 2nd paragraph, lines 6-8**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Delete this sentence; it repeats the end of p. 77.  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 78, last line**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “EPA 2012i” should be “EPA 2012f”  
**EPA Response:** Reference revised.

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**Location: Chapter 5, Page 79, 4th paragraph**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Data  
**Comment Type:** Peer Review

**Comment:** 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.”

**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 80, 1st paragraph**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** “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.

**EPA Response:** Text not revised because general resources, executive orders and regulations are provided in the second paragraph of the introduction.

---

**Location: Chapter 5, Page 80, 1st paragraph, line 4**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “only” should be deleted; existing data are discussed in the named sections (e.g., Table 5-3).

**EPA Response:** Text revised.

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**Location: Chapter 5, Page 80, last bullet on page**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to include the definition of the Superfund approach to calculating exposure point concentrations, along with appropriate references.

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**Location: Chapter 5, Page 81, Table 5-3**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** This is a useful, albeit truncated, list of possibilities.  
**EPA Response:** Text not revised because this statement does not provide recommendations to modify the text.

---

**Location: Chapter 5, Page 81, Table, row 1**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

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**Location: Chapter 5, Page 81, Table, row 4**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** How are “Crops and Livestock” a source of data? I suggest rewording to be like the other items in the list.  
**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Table revised.

---

**Location: Chapter 5, Page 82, bullets**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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, the type of acid used can also result in different findings (e.g., nitric, hydrofluoric)

**EPA Response:** Text not revised because the narrative provided by the reviewer (sieving the soil and extraction solutions) addresses the processing of the soil rather than analyzing the data. Methods for analyzing the data can be found in EPA's methods documents (e.g., lead guidance and others) that identify issues addressed in establishing data quality objectives and quality assurance project plans.

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**Location: Chapter 5, Page 82, line 6**

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**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** The direction of an aquifer's flow seems to be a strange example for the conditions data were collected on.

**EPA Response:** Figure updated to clarify the direction of the groundwater flow. The groundwater direction is important in determining the movement of contaminants, areas where additional sampling is needed and changes in concentration with distance from the source.

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**Location: Chapter 5, Page 84, 1st paragraph**

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**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 5, Page 84, 1st paragraph under table, lines 6-8**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** This sentence includes “need” and “needs.” Modify to remove one of these “need/s.” (same issue is in the second bullet on p. 85)  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 84, Table 5-4**

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**Submitter:** Clifford P. Weisel, Ph.D.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Add Breast milk to media column.  
**EPA Response:** Table revised.

**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Biomonitoring  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised and Table 5-4 updated.

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**Location: Chapter 5, Page 85, 1st and 2nd bullets**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Some sentences in these bullets repeat text at the bottom of p. 84.  
**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 86, 1st paragraph, line 3**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.”

**EPA Response:** Text revised. The summary data and mean values cited in these documents are based on published data and information from the general population (e.g., food survey findings) or sample populations from a specific group or region.

---

**Location: Chapter 5, Page 87, Table 5-5**

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**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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

**EPA Response:** Table revised.

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**Location: Chapter 5, Page 88, 5th bullet**

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**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Page 88 – under What methods are available for conducting observation studies – did you mean GPS rather than GIS?

**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 88, bullets**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** This section is confusing. Sub-bullets may help break it up and organize it so the hierarchy is more apparent.

**EPA Response:** Text revised.

---

**Location: Chapter 5, Page 88, bullets 2-4**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** These should be sub-bullets to the first bullet.  
**EPA Response:** Text revised.

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**Location: Chapter 5, Page 89, Section 5.4.6**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** Is this redundant with Chapter 6?  
**EPA Response:** The text in Chapter 5 does repeat information given in Chapter 6. Such repetition is appropriate because it allows the reader of Chapter 5 to easily compare and contrast the characteristics of data derived from models and other types of data. Chapter 5 includes a statement indicating that additional information is available in Chapter 6.

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**Location: Chapter 5, Page 90, Section 5.5**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** Is this redundant with Chapter 8?  
**EPA Response:** Text not revised because Section 5.5 discusses types of data, while Chapter 8 discusses how data are used.

---

**Location: Chapter 5, Page 95 (starting), Table 5-6**

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**Submitter:** Clifford P. Weisel, Ph.D.  
**Topic:** Data  
**Comment Type:** Peer Review  
**Comment:** It would be useful to provide years 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>

**EPA Response:** Table updated to include the two additional databases listed in comment. Additional information included to explain funding for RIOPA. The FDA link referencing the Total Diet Study was updated. The ATSDR Toxicological Profiles are included in Table 5-6.

---

**Location: Chapter 5, Pages 72-73, end 72, top 73**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:** “Biomarkers record the concentration of the chemical or its metabolites in biological media...” Does this mean that if you have x 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.

**EPA Response:** Text revised.

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**Location: Chapter 5, Pages 85-86, bullets**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** Is the Child-Specific EFH a good source to list here, or has it been superseded by the 2011 EFH?

**EPA Response:** Text not revised because the *Child-Specific Exposure Factors Handbook* was subsumed into the 2011 EFH. The child-specific exposure scenarios examples were included in the list of resources.

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**Location: Chapter 5, Section 5.1**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** 1. Page 61-63, Table 5-1 and associated text. The text describes the need to consider temporal and spatial extent of contamination. If Table 5-1 is provided as an example of these concepts, it would benefit from incorporating additional



relevant information, such as proximity to the source, wind or water flow direction, etc.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** 2. Page 63, second paragraph. When discussing evaluation of data, it is important to consider when the data were collected with regard to current relevance and the likely accuracy of the analytical methods. This should be added to this paragraph and Section 5.2 Data Quality.

**EPA Response:** Text not revised because the text already indicates the need to “consider the data collection timeframe, relevance to the exposure assessment being developed and changes in analytical methods (e.g., detection limits) over time.”

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**Location: Chapter 5, Section 5.2**

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**Submitter:** American Cleaning Institute (ACI)

**Topic:** Data

**Comment Type:** Public

**Comment:** In Section 5.2, there is a discussion which acknowledges the important role data quality plays in the exposure assessment but there is little detail regarding the means by which data quality is assessed and how it might be measured. We note that the World Health Organization (WHO) has published guidance regarding Uncertainty and Data Quality in Exposure Assessment. These are suitable for such a purpose and the Guidelines could adopt the terminology and approach described. Likewise, we acknowledge the discussion regarding data usability (Section 5.2.1) speaks conceptually to the use of data quality objectives to identify the proposed use of the available data. As part of the data quality assessment, there should be a statement of the limitations of the data within the exposure assessment.

Footnotes:

WHO. 2008. Uncertainty and Data Quality in Exposure Assessment. Part 1, Guidance Document on Characterizing and Communicating Uncertainty in Exposure Assessment; Part 2, Hallmarks of Data Quality in Chemical Exposure Assessment. Geneva, Switzerland: IPCS Harmonization Project, WHO.  
<http://www.inchem.org/documents/harmproj/harmproj/harmproj6.pdf>.

**EPA Response:** Text revised to include references provided by the commenter.

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**Location: Chapter 5, Section 5.2.1**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** 3. Page 64, Section 5.2.1. This section would benefit from some explicit discussion of the fit-for-purpose concept, particularly when discussing what data are needed and appropriate.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** Page 67. In Chapter 5 on aligning data with data quality objectives, the Guidelines state, “Determining whether existing data meet an exposure assessment’s DQOs is critical to assessing whether the data are useful for the assessment. Often, existing data do not completely align with the DQOs but do provide sufficient information. For example, air pollution sampling might be conducted as part of a network to track pollution trends, but these data also can be used to represent exposure concentrations at a regional or local level, depending on the locations of the samples.”

This example of using air pollution sampling data to document personal or population exposure measurements is concerning because it overlooks the fact that exposure misclassification has been a big problem in many of the air pollution epidemiology studies that have been used to justify new air quality guidelines. This statement should be accompanied by an explanation of the steps that can be taken to minimize exposure misclassification in air pollution observational studies.

**EPA Response:** Text revised to indicate the assessor needs to consider potential exposure misclassification when a participant is included in a population subgroup or category based on an observational or measurement error.

**Submitter:** The Teratology Society

**Topic:** Editorial

**Comment Type:** Public

**Comment:** In Chapter 5, Data for Exposure Assessment, on page 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.” This portion could be revised as: “The use of low-quality data in an exposure assessment should occur only in the absence of more reliable information; in these instances, the limitations and uncertainty of the data should be clearly communicated.”

**EPA Response:** Text not revised because the text describes considerations when using low-quality data including appropriate guidance.

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**Location: Chapter 5, Section 5.2.2**

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<b>Submitter:</b>	American Chemistry Council (ACC)
<b>Topic:</b>	Data
<b>Comment Type:</b>	Public
<b>Comment:</b>	<p>7. Page 71, Section 5.2.2. The paragraph at top of the page suggests that open source software (that can be edited by anyone) is a reliable source of statistical analysis tools. The basis for an EPA recommendation that open source software will enhance reproducibility and transparency in assessments is certainly not clear, and should be the subject of comment by peer reviewers. Unless an exposure assessor is both a programmer and a statistician, it is unlikely that correct application of statistical concepts will be reproducible under this suggestion. If EPA does endorse the use of open source code, it should issue a policy statement explaining its perspectives, including how it can be used reliably within its own IT firewalls and IT validation systems.</p>
<b>EPA Response:</b>	Text revised.
<b>Submitter:</b>	CropLife America (CLA)
<b>Topic:</b>	Data
<b>Comment Type:</b>	Public
<b>Comment:</b>	<p><b>**Pg 70, Addressing Non-detect Values:</b> “Robust methods generally assume a distribution only for the non-detect values rather than the entire dataset. The non-detect values are extrapolated using regression techniques. These methods do not assume that data above the detection limit follow a defined distribution that then can be applied to the non-detect values. These methods involve somewhat more data manipulation than distributional methods.” What are the statistical underpinnings for this approach? What references support this approach?</p> <p>In general, the strengths and weaknesses of the different approaches for assigning values to non-detect values should be described.</p>
<b>EPA Response:</b>	Text revised to include additional references for evaluating non-detects.

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**Location: Chapter 5, Sections 5.2.2 and 5.3.2**

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<b>Submitter:</b>	American Chemistry Council (ACC)
<b>Topic:</b>	Data
<b>Comment Type:</b>	Public
<b>Comment:</b>	<p>10. Page 72-73. The focus of section 5.5.2 and Figure 5-3 is on biologically persistent chemicals. The reason for this focus is unclear as non-persistent chemicals or metabolites may be of equal biological relevance.</p>

**EPA Response:** Text not revised because the approaches are applicable to both persistent and non-persistent chemicals.

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**Location: Chapter 5, Section 5.3.2**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** 11. Page 73, Figure 5-3. It is not clear why there are three purple lines for DNA adduct.

**EPA Response:** Text not revised because a reference to the paper is provided and added text explains that the different adducts provided in the figure are examples.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** 13. Page 73. The first two sentences in the last paragraph state: “Biomonitoring studies are used to address data gaps associated with possible exposures, baseline conditions and internal chemical or metabolite concentrations. Biomarkers of exposure can link a chemical in the environment with a health outcome.” This statement implies that biological monitoring can be used to establish causality, which is in fact very difficult to accomplish in most cases as both biologically measured metabolites and health endpoints may be non-specific. ACC recommends revising the second sentence to read: “Biomarkers of exposure alone cannot link a chemical in the environment with a health outcome,” similar to discussion in chapter 6 (page 117).

**EPA Response:** Text revised and references from CDC emphasizing the limitations of biomonitoring data in establishing disease causality added in Section 5.1.2.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** 12. Page 73. It is not clear whether the discussion of “biomarkers following a single exposure” at the metabolite or adduct level suggests that EPA is a proponent of the “one hit” theory of carcinogenesis (Figure 5.3).

**EPA Response:** Text not revised; the figure uses a single exposure scenario for the purposes of demonstration. Comparing decay curves following a single exposure event is easier than doing so for multiple exposure events. The use of this figure has no bearing on whether EPA is a proponent of the “one hit” theory of carcinogenesis.

**Submitter:** CropLife America (CLA)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Pg 74: “Also, biomonitoring data may not identify the relative contribution from different sources of exposure.”

While this seems like a small point, the words “may not” should be changed to “do not.” This is an important and well-recognized limitation of using biomonitoring as the basis for exposure assessment.

**EPA Response:** Text revised to include information from CDC regarding the limitations of using biomonitoring data to establish disease causality.

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**Location: Chapter 5, Sections 5.3 and 5.4**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** Page 74. EPA states “biomonitoring data demonstrate that human exposure to and absorption of a chemical actually have occurred.” This statement does not account for chemicals that are produced endogenously in the body or from metabolism. Related to this point, on page 84, the first bullet in Table 5-4 should be revised to state that biomonitoring requirements can “confirm presence of a chemical” (as opposed to confirming exposure to a chemical).

**EPA Response:** Text and table revised.

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**Location: Chapter 5, Section 5.3.3**

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**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** There are several important principles and practices reviewed in the 2004 Office of the Science Advisor staff paper that should be incorporated into the exposure assessment guidelines.

Specifically:

Section 5.3.3: This section provides a clear explanation of terms describing exposure distributions. The section, however, does not explicitly address “hypersensitive” individuals and the role of risk policy on establishing the upper end of the distribution as succinctly as the staff paper, which noted: “EPA considers the most sensitive individuals where there are data, but does not necessarily attempt to protect ‘hypersensitive’ individuals. The degree to which sensitive individuals are protected, or explicitly defined, may vary between

programs based on factors such as the need to balance risk reductions and costs as directed and constrained by statutory authority.” While the guidance does indicate that EPA “might incorporate a ‘high end’ to ensure adequate protection of exposed individuals, lifestages, groups or populations”, the guidance should more transparently describe the role of risk management and risk assessment policy in defining the degree of protection, and whether specific individuals, lifestages, or populations are included in the “high end estimate.” It is important to note that “hypersensitivity” is not necessarily limited to the dose-response portion of a risk assessment. For example, individuals with extremes in kidney function will exhibit a different distribution of blood and urine data than those with normal function.

**EPA Response:** Text not revised because the document includes a reference to EPA’s “Staff Paper” (*An Examination of EPA Risk Assessment Principles and Practices*) for additional details.

**Submitter:** U.S. Department of Defense (DoD)

**Topic:** Data

**Comment Type:** Public

**Comment:** “EPA might incorporate a “high-end” exposure level to ensure adequate protection of potentially exposed individuals/lifestages/groups/populations.” While this is reasonable for each route of exposure, combining such “high- end” exposures for cumulative exposures may result in a combination that cannot occur due to violation of conservation of mass or because the combination cannot occur in time or place to any individual.

Suggest adding a sentence such as: "While "high-end" exposure estimates care should be taken when combining such "high-end" exposures for cumulative or aggregate exposure estimates, as such combinations may result in a combination that cannot occur. While this is reasonable for each route of exposure, combining such "high-end" exposures for cumulative exposures may result in a combination that cannot occur due (1) to violation of conservation of mass or (2) because the combination cannot occur in the same time or place to any individual.

**EPA Response:** Text revised.

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**Location: Chapter 5, Section 5.4.1**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Data

**Comment Type:** Peer Review

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

**EPA Response:** Text not revised because the table indicates the differences in scale between these two categories; for example, defined area compared to individual exposures.

**Submitter:** American Chemistry Council (ACC)  
**Topic:** Data  
**Comment Type:** Public  
**Comment:** 18. Page 82 last bullet. ACC recommends adding discussion of the following:  
There is within a microenvironment of a room, the potential for further zones of exposure in close proximity to where a product is used. This is considered in several personal product use scenarios but could also be relevant to the use of arts and craft materials. These zones are smaller than the room and typically closer to a personal breathing zone in size.  
**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)  
**Topic:** Data  
**Comment Type:** Public  
**Comment:** 17. Page 81, Table 5-3. Consumer Product Sampling has a strong emphasis on food and water and very little is said about consumer products. This is confusing.  
**EPA Response:** Table revised.

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**Location: Chapter 5, Section 5.4.3**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT  
**Topic:** Biomonitoring  
**Comment Type:** Peer Review  
**Comment:** 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 Liroy 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, Liroy 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.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Page 85. ACC suggests revising language in the first paragraph as follows: “data may do not provide a direct link between an exposure source and a health effect...; concentrations can may, in some cases, confirm that exposures are occurring.”

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** 19. Page 84, Table 5-4, bullet 1: ACC suggests deleting the phrase “without establishing an exposure source” as this is adequately covered in the text.

**EPA Response:** Text not revised because this is an important point for the assessor to consider.

**Submitter:** CropLife America (CLA)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Pg 84: “However, biomonitoring may not identify a specific source of exposure or the period of exposure (e.g., years or days ago).”

Same comment as above: “may not” should be changed to read “does not”.

**EPA Response:** Text revised.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 5, Section 5.4.4**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** 21. Page 87, Table 5-5. The second row, second box, second bullet should be revised to read: “that could reduce/increase potential exposures”

**EPA Response:** Text revised.

**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Data

**Comment Type:** Public

**Comment:** Section 5.4.4: This section notes that use of defaults in risk assessments “raises concerns” especially with respect to EPA policy about using defaults. Concerns about “conservatism” have been raised by various stakeholders since the adoption of the risk assessment paradigm by federal government agencies. As noted in the staff report, the GAO has correctly observed that the used of assumptions (defaults) is unavoidable in risk assessment, which is an iterative and tiered process. Continuing to emphasizing (sic) the concerns about the use of defaults in this guidance diminishes the important role of transparency, stakeholder engagement, and peer review in the risk assessment process in defining an acceptable level of conservatism.

This section of the report provides an opportunity to revisit the fundamental principles, and emphasize that “inferential bridges” and “policy” are not only inherent in risk assessment, but essential to preventing “paralysis.” This section should emphasize, as explained in the staff report that EPA defaults are transparent, and generally based on scientific assessments. In cases where data is developed that show that default parameters or models are overly conservative (or not conservative enough), there are iteration and peer reviewed processes incorporated into EPA programs that allow for a refined assessment to proceed.

As noted in the 1983 NRC Risk Assessment in the Federal Government: Managing the Process, “when scientific uncertainty is encountered in the risk assessment process, inferential bridges are needed to allow the process to continue.” Risk assessment policy is defined as “the analytic choices that must be made in the course of a risk assessment. Such choices are based on both scientific and policy

considerations.” The report further notes “[t]hat a scientist makes the choices does not render the judgements devoid of policy implications.”

It is important to acknowledge that inferential bridges and risk assessment policy is required whether EPA, industry or an academic scholar selects the default model or assumption. With respect to the selection of default parameters and models, the guidance should emphasize the key principles, of transparency, iteration, and peer review, as well as the mechanisms available to stakeholders to contribute to the risk assessment process when there a concern that the default values are not “fit for purpose.”

**EPA Response:** Text revised.

**Submitter:** The Teratology Society

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Also in Chapter 5, Table 5-5 (page 87) lists three types of measurements that are common exposure factors: physical characteristics, activity frequency, and duration and intake rates. All three can be impacted for adult women during pregnancy, but neither the table nor the preceding paragraph includes this population.

**EPA Response:** Text revised.

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**Location: Chapter 5, Section 5.4.5**

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**Submitter:** American Chemistry Council (ACC) Section 7.2.2 and 7.2.5

**Topic:** Data

**Comment Type:** Public

**Comment:** Page 88. When discussing the Paperwork Reduction Act requirements, it is important to mention that the approval process is designed to ensure the quality and practical utility of the information that is being collected.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Page 87. The second sentence under 5.4.5 is unclear, as findings will not necessarily alter assumptions. ACC suggests changing the sentence to “findings can be used to evaluate assumptions about...”

**EPA Response:** Text revised.

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**Location: Chapter 5, Section 5.4.6**

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**Submitter:** U.S. Department of Defense (DoD)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** The text states: "(e.g., exposure models that estimate the cumulative impacts of exposures to multiple chemicals)". Under EPA's definition in this document, we believe the example should be to "aggregate" exposures, since it is combining multiple chemicals.

Suggest changing the adjective.

**EPA Response:** Text not revised because aggregate exposure is the exposure to a single chemical by multiple routes; cumulative exposure is exposure to more than one chemical by a single route or multiple routes.

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**Location: Chapter 5, Section 5.5**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to highlight the complex relationship of many factors.

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**Location: Chapter 5, Section 5.7**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Communication

**Comment Type:** Peer Review

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

**EPA Response:** Text not revised because this section refers to Chapter 9, where communication approaches are discussed.

**Submitter:** North American Metals Council (NAMC)

**Topic:** Data

**Comment Type:** Public

**Comment:** The U.S. Geological Survey (USGS) is listed in Table 5-6, Sources of Exposure Assessment Data, as a source for information on background levels of elements, including metals, in soils and other surficial materials. NAMC agrees that the use of USGS data may be useful as preliminary screens for metal exposures, but site-specific calculations may be necessary.

**EPA Response:** Table revised to include additional USGS information.

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**Location: Chapters 5 and 6**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** 13. The quality of biomonitoring data should be a key discussion topic in the Chapters 5 & 6, but it is not discussed.

**EPA Response:** Text revised to include link to CDC Biomonitoring Data Website for detailed information.

## Chapter 6. Computational Modeling for Exposure Assessments

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**Location: Chapter 6**

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:**

Text not revised because the current text indicates that model selection depends on the question(s) that need to be addressed. The current text indicates that model selection must begin with a conceptual model.

The text clearly indicates that more complex models might not be helpful and that model selection needs to be parsimonious and fit for purpose.

EPA agrees that adding additional figures to the text would increase the clarity of this and other points. The size of the document needs to be limited, however, to facilitate its use as a guideline.

Text has been added to address these points.

Such a comparison of strengths and limitations of the two approaches would be useful in detailed guidance for the use of probabilistic models, but such details are beyond the scope of this document.

The above approach is a minor variation of the approach currently described in the text; therefore, no significant revision is warranted.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** 10. Chapter 6. EPA should consider discussing compartment specific models (e.g. SkinPerm) that are designed and can be used to simulate/predict absorption and/or bioavailability of chemicals across different exposure routes.

**EPA Response:** Text revised to include modeling uptake.

Text not revised to include detailed discussion of this rapidly developing issue as it is beyond the scope of this document.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** 12. Chapter 6 contains the tacit assumption that PhD exposure assessors are the only ones qualified to select among available exposure assessment approaches and models. This approach ignores the fact that exposure assessors collaborate with modelers to select appropriate models, evaluate their output and test model modifications to ensure the exposure assessment is fit for purpose.

**EPA Response:** Text not revised because this comment appears to be a response to the following block of text: “Exposure assessors need to be aware that many available modeling applications could make exposure-modeling simulation appear deceptively simple. Any statistical modeling used to predict or estimate exposure is highly recommended to be conducted by, or in conjunction with, an expert in the discipline.”

This text is consistent with the point raised by the commenter. Exposure assessors need to work with experts when appropriate.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** Chapter 6 does not address the need to include physical, chemical and degradation properties of the chemical agent. These are very important and in the absence of measured data, there are tools for estimating these properties, and databases that contain measured properties for several chemicals. These data are needed in modeling exposure and in determining if the measured or modeled exposure concentrations are realistic. Appropriate references should be added to this chapter.

**EPA Response:** Text not revised because the chapter cites fate and transport models in multiple locations. The concepts in this comment are addressed by the fate component of the

cited models. Additional text on the specific processes that determine the fate of chemicals has been added in Chapters 3 and 6.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because EPA disagrees with the reviewer. Models are constantly being developed and falling into disuse. Many models developed in the 1980s and 90s are no longer meaningful for practical application because of the continual updates of computer operating systems. Because of the dynamic nature of the universe of available models, EPA has concluded that including a list of available models would not be a useful addition to this document. Instead, Table 6-1 is provided as a starting point for researching potential modeling software for use in specific assessments.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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).

**EPA Response:** Text revised to include a discussion of sub-models.



Text not revised to provide the level of detail in model selection and preference that are suggested because they are outside of the scope of this document.

Text revised to address specific recommendations and other comments. We agree with the commenter. Figure 6-3 emphasizes that the two processes of monitoring and modeling should interact in an iterative fashion.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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 are 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.

**EPA Response:** Text not revised because the modeling chapter currently refers to the text on data quality objectives in Chapter 5. What additional steps should be taken to tie the concepts together is not clear from the comment. The text clearly indicates that more complexity in a model will not necessarily result in better decisions. Models should be “fit for purpose.”

Text revised to include examples of geospatial models.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:**

Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter.

Text not revised to address “worst-case” scenarios because program-specific guidance is available and provided in Box 5-1 with program-specific references.

Text not revised because PBPK modeling is discussed in Chapter 6, Section 6.2.5, including appropriate references.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; no revision necessary because EPA agrees with this comment.

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**Location: Chapter 6, Page 103, 2nd paragraph in Section 6.1, line 7**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “and” instead of “or” makes more sense to this reviewer.

**EPA Response:** Text revised although we were unable to identify the instance of the word “or” in question, but the sentence has been revised to improve clarity.

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**Location: Chapter 6, Page 105, 1st paragraph in Section 6.2, line 1**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “selecting” would be a better word than “using” here.

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 105, 4th paragraph, 2nd sentence**

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**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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);

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 106, Table 6-1**

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**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** The rationale used to organize this table is not apparent to me. For example an overview paper is in the middle

**EPA Response:** Text not revised. Table 6-1 is a set of starting points for an exposure assessor looking for an exposure model. The overview paper is a significant source of information in several exposure models. Thus, including the reference in the table is appropriate.

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**Location: Chapter 6, Page 107, 2nd paragraph**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** The following sentence is odd and confusing... “Screening-level exposure assessments that use screening-level models are developed routinely in certain EPA programs.”

**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 107, last paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text not revised because E-FAST falls on the simple end of the continuum.

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**Location: Chapter 6, Page 107, Section 6.2.2**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** I have some difficulty with this section as outlined above in my main comments on the Chapter.

**EPA Response:** Text not revised because no specific recommendations were provided in this comment.

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**Location: Chapter 6, Page 108, 1st paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** Sensitivity analysis can be performed using deterministic approaches through brute force variation of model inputs.

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 108, Figure 6-1**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** This Figure is simplistic, but does give a stepping-off point for discussion

**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on the figure presentation.

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**Location: Chapter 6, Page 108, figure endnote**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Add space after “al.”

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 108, last paragraph, last sentence**

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**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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].

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 109, Figure 6-2**

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**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** Single value output graph: Question: What is D in the abscissa? It appears to be an error

**EPA Response:** Figure revised.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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 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.

**EPA Response:** Figure not revised. We agree that Figure 6-2 does not reflect the fact that many probabilistic analyses select values from empirical data sets that do not follow any specific type of distribution. We also agree that the diagrams for the frequency and cumulative frequency do not correspond. That is why the shape of the cumulative distribution of an output with the frequency distribution given in the picture would look different. The figure and its components, however, are meant to represent images of the types of distributions and not actual inputs or outputs from a specific model run. The components are best viewed as icons or graphical representations.

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**Location: Chapter 6, Page 110, footnote**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Should this be “chemical concentrations in environmental media”?

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 110, last paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review



**Comment:** There needs to be an expansion of what is meant by "... Some analyses might even involve simulations to evaluate temporal and spatial variability."

**EPA Response:** Text not revised because this is a reference to a microexposure event modeling.

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**Location: Chapter 6, Page 111, 1st paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the reviewer is correct that Monte Carlo modeling is not necessary for performing sensitivity analyses. That comparisons of input distributions to output distributions from Monte Carlo modeling is a useful approach for sensitivity analyses, however, is still true.

Text revised to remove the term 1-D Monte Carlo analysis from this document. It is now just referred to as Monte Carlo analysis.

Text not revised because the text on the differences between Monte Carlo modeling and 2-D Monte Carlo are clearly stated in the text. The text also indicates that Monte Carlo analyses can consider variation, uncertainty, or both.

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**Location: Chapter 6, Page 111, 2nd paragraph**

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**Submitter:** Alan H. Stern, Dr. P.H., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** After, "...variables are selected randomly" add, "from input probabilistic distributions."

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 112, 3rd bullet**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the strengths and limitations of expert elicitation and the decision on when it should be used are valid issues. These issues, however, are beyond the scope of this document.

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**Location: Chapter 6, Page 112, 4th line**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Should say “reasonably constant over time”

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 113, 1st paragraph**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “processes in the source-to-exposure continuum.” I suggest rephrasing this.

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review  
**Comment:** I suggest adding a word: “The emphasis here is on physical-based...”  
**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** What does “physical-based” mean here?  
**EPA Response:** Text revised.

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**Location: Chapter 6, Page 113, 2nd bullet**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** How does one get from concentrations to exposures?  
**EPA Response:** Text revised.

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**Location: Chapter 6, Page 113, last paragraph**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** 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?  
**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 113-114, end 113, top 114**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Modeling  
**Comment Type:** Peer Review

**Comment:** Why are these two particular models mentioned here, while no water-centric models are mentioned?

**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 114, 6th line in paragraph**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Should be... hazardous “air” pollutants

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 114, last paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** Can the text differentiate between SHEDS-Air and SHEDS?

**EPA Response:** Text revised.

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**Location: Chapter 6, Page 115**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** CHAD. This database is now quite old. Is it time for an update?

**EPA Response:** Text not revised because, although research is ongoing in this area, the CHAD data are the most recent. EPA’s current efforts and future plans for activity patterns are beyond the scope of this document. Two versions of CHAD are available for download on the EPA website: CHAD-Master contains human activity data from 22 different studies performed in 1982–2010, and CHAD-2000 is the original CHAD database in Microsoft Access Format. It contains detailed human activity data from 12 studies performed in 1982–1998.

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**Location: Chapter 6, Page 115, 2nd paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text revised.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** Is this not redundant with earlier sections?

**EPA Response:** Text not revised because the repetition of text in Chapters 6 and 3 facilitates access to specific topics. Some repetition of text is appropriate.

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**Location: Chapter 6, Page 116, 3rd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** Is not the Draft Protocol a bit dated? The pesticides used and their use patterns have changed substantially in the last 15 years

**EPA Response:** Text not revised because the concepts described in the text are still valid and relevant.

---

**Location: Chapter 6, Page 117, 2nd paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Bolded text should be “Dose Estimation Models,” based on the bullets on page 113.

**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 117, 3rd paragraph**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** The sentence beginning “Chemicals or their metabolites commonly...” is confusing as written.

**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 117, 3rd paragraph, line 4**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** I suggest changing is to function as or constitute to address the plural noun biomarkers transitioning to the singular noun tool.

**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 117, long paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The sentence on the characteristics of a good biomarker repeat text from the top of page 73.

**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 118, top**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** “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?

**EPA Response:** Text removed.

---

**Location: Chapter 6, Page 119, 2nd paragraph**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised here and in Chapter 5.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** “timing of the accumulation period and urine volumes...” How is this done? By taking the first urination upon waking in the morning?

**EPA Response:** Text not revised because the survey asks the participant to measure the total volume of the void that is sampled. The user is also asked to report the time before last void. This level of detail is beyond the scope of this document.

---

**Location: Chapter 6, Page 119, 3rd paragraph**

---

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 119, center**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** End of paragraph, “inherent assumptions.” Such as? Does this mean assumptions such as linear responses, instantaneous mixing within each compartment, etc.?

**EPA Response:** Text not revised. In response to the question, these are examples of such assumptions.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** A compartment “not physiologically defined...,” such as volume of distribution. How is the volume of distribution defined, if not physiologically?

**EPA Response:** Text not revised because a question is posed. In response to the question, the volume of distribution is frequently defined empirically in animal and human studies by comparing blood concentrations of a chemical to an administered dose. Such measurements do not indicate which tissues or organs are involved in the distribution of the substance.

---

**Location: Chapter 6, Page 119, last 2 lines**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “...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.

**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 119, last 4 lines**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “Important to note, however, is that...” I suggest rewording this. It’s a bit awkward.

**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 119, last line**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “PBPK models are recommended to:” This is a bit awkward, and I suggest changing it to: “EPA recommends the following:”

**EPA Response:** Text revised.



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**Location: Chapter 6, Page 120, 1st-3rd paragraphs**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Purpose and Scope  
**Comment Type:** Peer Review  
**Comment:** The Executive Summary and Introduction both say that this topic will not be included in the document. Therefore, these paragraphs should be deleted.  
**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 120, bullets**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** These require lots of data that may not be available for most compounds and inhuman subjects.  
**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 120, paragraph after bullets**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** “Prioritizing the need for animal testing.” I wasn’t sure what this means.  
Targeting chemicals for animal testing?  
**EPA Response:** Text not revised because this refers to identifying chemicals for animal testing.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised because the SHEDS-HT model’s predictions are more uncertain than those from earlier SHEDS models (i.e., SHEDS- Multimedia) because of

simplifications made in SHEDS-HT. Thus we are “getting more uncertainty” and getting more coverage of thousands of chemicals with in vitro data.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** “other purposes.” What does this refer to?  
**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 120, top of page**

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**Submitter:** Clifford P. Weisel, Ph.D.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** Bullet points should also include issues of age, gender and polymorphisms  
**EPA Response:** Text revised.

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**Location: Chapter 6, Page 121, 3rd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** I think it is fair to question the utility of computationally complex models that cannot be validated.  
**EPA Response:** Text revised.

---

**Location: Chapter 6, Page 121, long paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** 2nd line: “data (e.g., other model predictions...) Do model predictions qualify as “data?”  
**EPA Response:** Text not revised because, although such predictions are not empirical data, they *are* data.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

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**Location: Chapter 6, Page 122, Figure 6-3**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** The words “Select Model” are not bold; all if the other text is bold.  
**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** 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?”  
**EPA Response:** Text revised.

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**Location: Chapter 6, Page 124, 1st paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** 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.

**EPA Response:** Text not revised because text regarding DQOs is presented in Chapter 5. The issue of evaluation without a comparison to empirical data is discussed in the text. Such methods for evaluation of models includes the consideration of the quality of the science in the model, the quality of the data used to parameterize the model, and the potential for determining the uncertainty in individual components of the model. Finally, quantitative models of uncertainty can provide insight on these issues.

---

**Location: Chapter 6, Page 124, 3rd paragraph, line 1**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the specific reference is given here. The summary box on page 154 cites a single reference that provides definitions for multiple terms. Thus the two separate references are appropriate.

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**Location: Chapter 6, Page 125, 1st paragraph**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** What is the benefit of using these more complicated sensitivity analyses and stepwise regressions?

**EPA Response:** Text not revised because such analyses allow the modeler to identify with greater certainty which model inputs should be the focus of model refinement. If the critical inputs are well characterized, the confidence in the model predictions is increased.

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**Location: Chapter 6, Page 22, Section 6.3.1 (and others)**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** I suggest not hyphenating risk management. There are a few other instances with the hyphen in the document, but many more without it.

**EPA Response:** Text revised.

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**Location: Chapter 6, Section 6.2.1**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** 1. Page 106, Table 6-1. The models on some of these sites are not up to date and cannot run on Windows computers. An evaluation needs to be made.

**EPA Response:** Text not revised because model availability is a challenge. The websites cited are intended to be reasonable starting points for searching for potential models. They are not a certification that all models at the sites meet a given level of usefulness.

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**Location: Chapter 6, Section 6.2.2**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Page 108, Figure 6-1, right hand access label. ACC suggests revising to read: "Greater decision-making confidence needs."

**EPA Response:** Text revised to remove the word "confidence."  
Other text not revised because keeping the text general more appropriate.

  

**Submitter:** American Chemistry Council (ACC)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** Pages 110-112 on Probabilistic Models. ACC suggests that this section mention the importance of making sure the assessor considers any correlations between variables/factors used in modeling exposure, since these correlations can result in erroneous estimates either high or low.

**EPA Response:** Text not revised because this commenter is correct in their assertion. This point, like many others, should be included in guidance that is specific to the use of probabilistic models, but such specific details are beyond the scope of this document.

  

**Submitter:** U.S. Department of Defense (DoD)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** In the section "Deterministic Models", it would be useful to remind the reader that the presentation of just one set of parameters, especially those based primarily on

"high-ends" of the distribution, can poorly characterize the range of possible exposures.

Suggest as EPA's 2005 cancer guidelines recommends, that if deterministic models are used, that at least 2 estimates, one of the "high-end" as well as a measure of central estimates of exposures, e.g., the median, also be presented to provide the decision-maker with a quick measure of the range of possible exposures. This discussion could also reference back to Box 5-2. "Terms Describing Exposure Distributions" as well as Section 5.3.3 which describes similar practice in the cited reference EPA 2004b.

**EPA Response:** Text not revised because Chapter 6 focuses on the technical issues related to modeling and not on guidance for how specific types of models should be used in specific decision making processes.

Text revised to include a discussion on the use of deterministic models to determine typical and upper bound estimates.

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**Location: Chapter 6, Section 6.2.3**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** Page 117, Exposure and Dose Estimation Using human biomonitoring data: The statement that biomonitoring "is an integrated measurement of exposure of a chemical from all sources and routes at a point in time," is not wholly accurate because a biomonitoring measurement does not tell you where the person is in the exposure time course. It is also important to mention that human biomonitoring is useful in exposure reconstruction when it is accompanied with contextual information (e.g., timing and intensity of exposure events including food consumption, personal care products application, etc.).

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** Page 118. The draft reflects poor understanding of simple biological variability, which explains why measured biomarker concentrations are not consistent.

**EPA Response:** Text revised to improve clarity.

Text regarding biological variability not revised because the basis for this comment is unclear. As a result, providing a specific response to the comment is difficult. We note that the document already devotes considerable text to the discussion of human variability. The issue of temporal variability is also discussed in the text.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** Page 119. The draft overstates the availability of PK data in humans.

**EPA Response:** Text not revised because what the commenter is referring to in this comment is not clear. Text regarding PK and biomonitoring data in humans is limited, and the text emphasizes that the field of PK modeling is rapidly changing.

  

**Submitter:** Consumer Specialty Products Association (CSPA)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** CSPA requests that clarification be added to the section High Throughput Exposure Models (pg 134 of .pdf file) to indicate that this project is not intended to refine the uncertainty in a risk assessment, rather to more clearly interpret and integrate in vitro screening data for hazard assessment and subsequent risk characterization.

**EPA Response:** Text not revised because this point is clearly made in the current text.

  

**Submitter:** Consumer Specialty Products Association (CSPA)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** CSPA notes that “Toxicodynamic” should be changed to “Toxicokinetic” in the section on Simple PK Models on page 119 (page 133 of pdf) of guidance for consistency – this is the only occurrence[occurrence] of “toxicodynamic”.

**EPA Response:** Text revised.

  

**Submitter:** CropLife America (CLA)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** \*\*Pg 118, Reverse Dosimetry: The Guidelines appear to be recommending a creatinine correction approach to addressing problems with urinary dilution and biomonitoring interpretation. However, issues and limitations associated with use of creatinine correction have been well-documented (LaKind and Naiman 2015; Lorber et al. 2011; Weaver et al. 2014) and other approaches to addressing urine dilution have been described (Sauvé et al. 2015; Yeh et al. 2015). This information should be included in the Guidelines.

**EPA Response:** Text revised.

**Submitter:** CropLife America (CLA)  
**Topic:** Modeling  
**Comment Type:** Public  
**Comment:** \*\*Pg 120, High-Throughput Exposure Models: Cautionary information was given for use of PBPK models, and similar information is needed here as this approach is increasingly being used for exposure assessments. It is noted that this approach has uses for prioritization for animal testing and “other purposes”. What are the other (or some other) purposes?  
**EPA Response:** Text revised.

**Submitter:** CropLife America (CLA)  
**Topic:** Modeling  
**Comment Type:** Public  
**Comment:** \*\*Pg 120: “To use these data properly requires screening estimates of the aggregate exposures to the chemicals.”  
What is meant by using the data “properly”?  
What kinds of aggregate exposure estimates are needed? It is worth noting that a recent publication found that “ToxCast PPAR $\gamma$  and RXR $\alpha$  assays do not correlate well with laboratory measurements of PPAR $\gamma$  and RXR $\alpha$  activity” suggesting limitations to the ToxCast data (Janesick et al. 2016).  
Before linking exposure estimates to Toxcast outputs, it appears that further verification for this approach is needed  
**EPA Response:** Text revised to clarify that prioritizing based on risk requires data on exposure.  
Text not revised regarding discussions on the ToxCast data and use in regulatory decision making is beyond the scope of this document.

**Submitter:** CropLife America (CLA)  
**Topic:** Modeling  
**Comment Type:** Public  
**Comment:** \*\*Pg 120: “An initial effort applied SHEDS-HT to 2,507 organic chemicals associated with consumer products and agricultural pesticides. The model addressed exposure associated with the use of commercial products (near field sources) and dietary exposures from agricultural pesticide use. The SHEDS-HT approach has the advantage of generating estimates of the distributions of aggregate exposures across populations of different ages.” How did SHEDS-HT perform? Were the results compared to other estimates of exposure?  
**EPA Response:** Text not revised because the purpose of this document is to provide examples of models that illustrate certain categories. Providing details on the models’



predictions, their appropriateness for any given use and how they have been evaluated is beyond the scope of this document.

**Submitter:** The Teratology Society

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** Also Chapter 5, pages 117 -119 discusses biomonitoring and PK/PBPK modeling. Cord blood and/or urine from pregnant women for biomonitoring and modeling during pregnancy could be included in this section; discussion of the pros and cons of the selection of these biofluids would also be advantageous.

**EPA Response:** Text added to indicate that cord blood and urine can be used to address in utero and perinatal exposures. The current text does include some discussion of strengths of various monitoring biofluids, and further revisions were not made.

Additional information on this point, however, is beyond the scope of this document.

**Submitter:** Virginia Department of Environmental Quality (DEQ)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** Section 6.2.3, High-Throughput Exposure Models: For in vitro/in vivo models, please add a discussion of extrapolating these data to human populations and also about need for using experimental versus validated and/or standard methods. For SHEDS-HT and similar models, include discussions on limitations, common pitfalls, sensitive parameters, and need to data quality to get reliable results as well as validate these models.

**EPA Response:** Text not revised because a discussion of the points in this comment is beyond the scope of this document. The Guidelines are not meant to provide detailed information on any specific model. The models listed here are presented as examples of different types of models and how they can be used in exposure assessments.

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**Location: Chapter 6, Section 6.2.3; Chapter 8, Section 8.3**

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**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** Section 6.2.3 and Section 8.3: Section 6.2.3 discusses the use of integrated fate and transport models to inform agency decision making. Figure 8-2 shows a schematic of the tiered approach to data uncertainty with increasing levels of complexity. As the exposure scientist increases the complexity of the assessment, the overall

transparency of the assessment typically decreases because most stakeholders have difficulty relating distributions of input and output parameters to the “real world.” Complex multimedia models may have 10 or more sub-models, making it difficult to adequately peer review the assessment when point estimates are not available.

I served on the public peer review panel for EPA’s Approach for Estimating Exposures and Incremental Health Effects from Lead due to Renovation, Repair, and Painting Activities in Public and Commercial Buildings. This approach represented a commitment of EPA to adopting state of the art methodologies. The approach, however, was challenging to peer review because the current guidance from EPA focuses on transparency in communication of the inputs and output of modeling assessments rather than communication of the intermediate steps. In complex linked models, there are several intermediary model estimates, often over time in multiple media.

Currently, there is little guidance regarding the minimum set of intermediate information that should be communicated in complex assessments that rely on linked models to ensure clear communication between users and stakeholders. For example, a complex model of metal dose may include exposure sources such as dietary intake, incidental dust ingestion and many other pathways. Each of these sources may require individual models, all subject to model selection uncertainty, parameter uncertainty and parameter variability. In a complex model, it may be difficult to understand how the model-predicted household dust concentrations compare to “real world” measured data unless the model developers take specific steps to incorporate transparency into model design and reporting.

As complex assessments become more common, it will be important for EPA to develop guidelines protective of the principle of transparency that ensure that interested stakeholders are able to participate and understand not only the high level input and output, but also the individual sub-units that comprise larger modeling efforts. It is recommended that the draft guidelines incorporate specific discussion about the importance of incorporating transparency of intermediate model estimations as a fundamental design element of higher tier assessments. In the longer term, it is recommended that specific guidance or principles describing approaches to transparency in complex exposure/risk assessments be developed. Development of these guidelines will be particularly important as EPA adopts high-throughput methodologies.

Specific examples of transparency elements that can be incorporated into probabilistic linked models include:

Presentation of example calculations and point estimate inputs and outputs for all model sub-units to provide context to the types of parameter combinations that lead to low, medium and high exposure or dose (see for example the use of both point estimates and probabilistic techniques for hair spray exposure scenarios in Sahmel et al. 2009);

Addressing model uncertainty by showing how a more simple approach can be used to bound the upper and lower bound (see for example the bounding evaluation

of PFOA release as particle or vapor in Figure 9 and simple groundwater model in Figure 10 of Paustenbach 2007);

Creating an information management system that facilitates an efficient means of reviewing the technical basis of a model element, such as particulate matter emission factor or consumer product release estimate;

Making available to stakeholders a working version of the model (using simplifications or extrapolations if necessary) that will allow stakeholders to ask “what if” questions and evaluate how changes in parameters affect predicted exposure;

Explicitly evaluating whether the input parameter combinations representing the low and high extremes of exposure represent high end, bounding, or impossible conditions; and

Archiving and making available upon request the input and output parameters of each Monte Carlo iteration.

**EPA Response:** Text not revised because the commenter raises significant points in this comment. Many of the recommendations are likely to be useful in the Agency’s development of more complex models. The process of developing and validating a new model or modifying and evaluating an existing model and the establishment of specific requirements, however, are beyond the scope of this document. EPA notes that many of the issues raised in this comment are addressed in recent guidance on the development of models at <https://playbook.cio.gov/>.

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**Location: Chapter 6, Section 6.3**

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**Submitter:** CropLife America (CLA)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** \*\*Pg 121: “Although complex computational models typically cannot be validated, module-specific predictions can be evaluated against available measurements or alternative model predictions” “Validation is the task of demonstrating that the model is a reasonable representation of the actual system” (<http://www.inf.ed.ac.uk/teaching/courses/ms/notes/note14.pdf>). The Guidelines should explain the implications for the inability to validate complex computations models, as EPA is using these kind of models with increasing frequency.

**EPA Response:** Text revised.

**Submitter:** Virginia Department of Environmental Quality (DEQ)

**Topic:** Modeling

**Comment Type:** Public

**Comment:** Section 6.3: While implied in this section, model validation, sensitivity analysis, and verification are part of model development and vetting that should be done

prior to performing the study. Please include a discussion on this important aspect of model evaluation. Additional information or text boxes that present key aspects of what makes a model effective or reliable would also be of significant assistance to readers.

**EPA Response:** Text revised.

## Chapter 7. Planning and Implementing an Observational Human Exposure Measurement Study

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### Location: Chapter 7

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Power calculations. Text revised.

Effect size. Text not revised because the intent of the text is to help the reader understand that effect size can be used to determine the appropriate sample size for a study. More details on effect size would be found in general statistics books.

Compensation and incentives. Text revised.

Some redundancy is found in the chapters of the document to help the user of the document. Text not revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Observational Studies

**Comment Type:** Public

**Comment:** Chapter 7 provides a very high level discussion of observational human exposure measurement studies. However, it provides limited practical guidance and several key concepts are absent from the discussion. The references provided are primarily examples of studies, and are not instructional.

**EPA Response:** Text not revised because the chapter is not intended to provide an instructional manual on how to conduct an observational human exposure measurement study.

The intent of the chapter is to provide a high level overview of the scientific and ethical considerations needed to conduct these types of studies and to provide references.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to add a sentence at the end of the opening paragraph to Chapter 7, which states “These types of studies do not intentionally introduce agents or other stressors into people’s environments.” Additionally, the first sentence of Chapter 7 is responsive to the intent of the comment.

Text revised to add a caution statement to Section 7.2.11 to support the intent of the comment on a researcher’s influencing a participant’s behavior.

Text not revised because the text states that the data from an observational human exposure measurement study can be used to refine exposure and dose models. The text is correct as written.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the commenter recognizes the work of the writing team.  
Text not revised because the second paragraph in Section 7.1 supports the intent of the comment. “The data collected in the study, however, need to be compatible with the data needs of the model of interest.” And, “An iterative relationship exists between the information derived from observational human exposure measurement studies and exposure and dose models (see Section 6.2).”

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Box 7-1 updated.  
Nieuwenhuijsen (2015) was added to Chapter 2. A statement on the relationship between observational human exposure measurement studies and epidemiological studies was added in Section 7.1.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the document includes references to IRBs and other oversight bodies involved in observational human exposure measurement studies. More information can be found in the included references.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** No revision necessary because the commenter compliments the technical panel on a well-written chapter.

Effect size. Text not revised. The definition of effect size in the document is correct. The comment takes the effect size out of context. The three paragraphs in Section 7.2.3 provide several pieces of information that should be considered together to address sample size. Section 7.2.3 addresses the intent of the comment.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review



**Comment:** 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.

**EPA Response:** Text not revised because the text already includes a discussion of engaging stakeholders in the study.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the commenter recognizes the work of the writing team.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the commenter supports the content of Section 7.2 and reiterates that in her comment.

Section 7.2.3. Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 7, Page 127, 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** Can an “observational human exposure measurement study” include, for example, a study in which food items are sampled and analyzed?

**EPA Response:** Text not revised because the text states that duplicate diet samples can be collected, sampled and analyzed as part of an observational human exposure measurement study.

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**Location: Chapter 7, Page 127, 3rd paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:** “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?)

**EPA Response:** Text revised.

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**Location: Chapter 7, Page 128, 1st paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** More generally, one should include IRBs at all locations, not just these.

**EPA Response:** Text not revised because IRBs are discussed in the chapter.

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**Location: Chapter 7, Page 128, 1st paragraph, lines 1-6**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Strike the second sentence (lines 4-6, as it is a repeat of the first sentence (lines 1-4.)

**EPA Response:** Text revised.

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**Location: Chapter 7, Page 128, 2nd paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Remove extra spaces after the first sentence.

**EPA Response:** Text revised.

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**Location: Chapter 7, Page 129, last paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** I am not sure how these studies, out of the hundreds of sample size studies done, were selected for referencing.

**EPA Response:** Text not revised because these studies were selected as representative of the types of studies that the agency might use. EPA acknowledges that this is not a comprehensive listing of human studies because the word “examples” is used in the title of Box 7-1.

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**Location: Chapter 7, Page 129, Section 7.2.3, 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** “power that the study can achieve.” Does this refer to statistical “power,” or something else?

**EPA Response:** Text revised.

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**Location: Chapter 7, Page 129, 4th paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** Discussion of budget/sample size is key

**EPA Response:** Text not revised because a discussion of budget and statistical evaluation is included in the chapter.

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**Location: Chapter 7, Page 131, 4th paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** Sample storage procedures are part of both protocol and Chain of Custody (CoC) issues

**EPA Response:** Text not revised because what the reviewer is stating can happen is not clear. Chapter 7 does include a discussion on chain-of-custody procedures.

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**Location: Chapter 7, Page 133, 3rd paragraph**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** 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”?

**EPA Response:** Text not revised because, as noted in the Preface and Introduction, the primary audience is EPA scientists, engineers, and policy/regulatory staff and contractors who perform this type of work for the agency.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** It is not only EPA that has interest in these ethical issues, yet the text would suggest this is the case.

**EPA Response:** Text revised to read “In conducting these studies, all scientists (regardless of affiliation) should endeavor to apply the most current scientifically valid approaches, while recognizing the special responsibilities regarding the ethical issues that sometimes arise when conducting these studies.”

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**Location: Chapter 7, Page 133ff, Section 7.2.10**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** This entire section focuses on regulation rather than the “science” of ethical research. I think the focus should be on the latter.

**EPA Response:** Text not revised because Section 7.2.10 focuses on considerations related to human subjects research.

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**Location: Chapter 7, Page 134, 3rd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review

**Comment:** It is not always either possible or feasible to collect personal samples of every type.

**EPA Response:** Text not revised because the text discusses several factors to consider when designing a study (e.g., resources, analytical methods), which could limit data collection.

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**Location: Chapter 7, Page 135, 3rd paragraph**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Consider having a paragraph break at “In addition to environmental samples...”

**EPA Response:** Text revised.

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**Location: Chapter 7, Page 136, 1st paragraph, last line**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Revise to read “....Sciences Institute’s framework for children’s risk assessment (Olin and Sonawane 2003).”

**EPA Response:** Text revised.

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**Location: Chapter 7, Page 136, Section 7.2.13**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Observational Studies

**Comment Type:** Peer Review  
**Comment:** Plan first- then design database.  
**EPA Response:** Text not revised because a specific change is not identified.

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**Location: Chapter 7, Page 137, 2nd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Observational Studies  
**Comment Type:** Peer Review  
**Comment:** Can use the main changes in the database design and implementation in the NCS as an example of what can happen  
**EPA Response:** Text not revised because what the reviewer is stating can happen is not clear. Several examples of observational human exposure measurement studies are provided throughout Chapter 7.

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**Location: Chapter 7, Page 137, 3rd paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Observational Studies  
**Comment Type:** Peer Review  
**Comment:** The TEAM Study is 30 years old.  
**EPA Response:** Text not revised; no revision necessary because this is a statement.

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**Location: Chapter 7, Section 7.1**

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**Submitter:** CropLife America (CLA)  
**Topic:** Biomonitoring  
**Comment Type:** Public  
**Comment:** Pg 127: Human measurement studies are increasingly relying on biomonitoring as the source of exposure data; biomonitoring should be included here.  
**EPA Response:** Text not revised because Section 7.1 includes discussion of biomarkers and biomonitoring. Additional discussions on this topic are included in Chapter 5 and Chapter 6.

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**Location: Chapter 7, Section 7.2.10**

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**Submitter:** American Chemistry Council (ACC)  
**Topic:** Observational Studies

**Comment Type:** Public

**Comment:** Section 7.2.10 Human Subjects Consideration. This section appears to state that an IC and IRB review are required for all studies including questionnaires regarding habits and practices. EPA should clarify whether this interpretation is intended.

**EPA Response:** Text not revised because the text states when an IRB review is required and when an Information Collection Request is required.

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**Location: Chapter 7, Section 7.2.11**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Observational Studies

**Comment Type:** Public

**Comment:** 7. Page 135. Section 7.2.11 states “[b]iological samples are used to measure the absorbed dose of the chemical of interest.” This statement excludes consideration of metabolites, which may be better indicators of exposure- related risk.

**EPA Response:** Text not revised because biological samples can be analyzed for parent or metabolite compounds. Statement is correct as written.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Observational Studies

**Comment Type:** Public

**Comment:** Section 7.2.11. This section should include a discussion of the need to determine appropriate preservation methods for samples. In fact, this should be included in several of the places where sampling and data quality are discussed.

**EPA Response:** Text revised to include “preservation methods” when discussing field sample collection.

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**Location: Chapter 7, Section 7.2.6**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Observational Studies

**Comment Type:** Public

**Comment:** 3. Page 130. Section 7.2.6 introduces the concept that the sampling and analytical methods should be “sufficiently accurate, precise and sensitive...” ACC believes EPA should provide additional detailed guidance on the determination of acceptability.

**EPA Response:** Text not revised because expectations on the accuracy, precision and sensitivity of the methods will vary with the DQOs established during the planning and scoping and problem formulation stage of the assessment.



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**Location: Chapter 7, Section 7.2.7**

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**Submitter:** CropLife America (CLA)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** Pg 131, Section 7.2.7: Here and throughout this chapter, information on biomonitoring should be included. In terms of storage of materials, this is addressed for biomonitoring by LaKind et al. (2014) and others.

**EPA Response:** Text not revised because Section 7.2.7 addresses chain-of-custody, storage and data management.

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**Location: Chapter 7, Section 7.2.9**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Observational Studies

**Comment Type:** Public

**Comment:** 5. Page 132. Section 7.2.9 notes that “in some instances” it may be useful to engage stakeholders to participate in planning and scoping. EPA’s HHRA Framework recognizes that stakeholders should always be engaged, and this concept must be incorporated into the draft.

**EPA Response:** Text revised to be consistent with the HHRA Framework.

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**Location: Chapter 7, Section 7.3.3**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

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**Location: Chapter 7, Section 7.4**

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**Submitter:** American Chemistry Council (ACC)  
**Topic:** Observational Studies  
**Comment Type:** Public  
**Comment:** 9. Section 7.4. ACC suggests that EPA add a bullet on database structure to capture and allow analyzing of field study data.  
**EPA Response:** Text revised.

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**Location: Chapter 7, Section 7.5**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Peer Review  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised because consideration of the use of peer review and reference to the Peer Review Handbook are provided in Sections 5.2 and 7.5.

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**Location: Chapter 7, Sections 7.2.6 and 7.2.7**

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**Submitter:** American Chemistry Council (ACC)  
**Topic:** Observational Studies  
**Comment Type:** Public  
**Comment:** Pages 131-132, section 7.2.6-7. During study design, data quality and data management protocols including sample validity criteria should be identified or developed (e.g., void protocol).  
**EPA Response:** Text not revised because data management procedures are discussed in Section 7.2.7.

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**Location: Chapter 7, Sections 7.7.2 and 7.7.5**

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**Submitter:** American Chemistry Council (ACC)  
**Topic:** Observational Studies  
**Comment Type:** Public

**Comment:** Section 7.2.2 and 7.2.5. Identification of critical data elements and eligibility criteria do not discuss selection biases which could significantly impact results.

**EPA Response:** Text not revised because, during the process of establishing eligibility criteria, selection bias is addressed.

## Chapter 8. Uncertainty and Variability for Exposure Assessments

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### Location: Chapter 8

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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 Monte 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.

**EPA Response:** Text not revised because Sections 6.2.2 and 6.3.4 discuss considerations in selecting models based on available data.

Text not revised since qualitative uncertainty analysis options are discussed in Section 8.1.1.

Box 8-1 revised to address comment.

Questions regarding decision uncertainty revised and reordered to address comment.

Section 8.3.2 revised to emphasize the conservative nature of the assumptions to exclude exposure pathways and scenarios that pose little risk.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** Chapter 8 is an extremely important discussion about uncertainty and variability in exposure assessment. ACC believes that transparency about uncertainty and variability in risk assessment is critical. EPA has consistently stressed the need to characterize uncertainty appropriately (using tiered and fit-for-purpose approaches) and the need for uncertainty evaluations in exposure assessment should be no different. Sensitivity analyses will be extremely useful to help assessors and stakeholders understand the key parameters in an exposure assessment. EPA has recognized this and provides some very helpful considerations throughout the chapter. Indeed these considerations and recommendations, including important recommendations on communicating the results of an uncertainty and variability evaluation, should be adopted by EPA exposure assessors and integrated in EPA risk assessments. ACC recommends that EPA highlight its key considerations and recommendations on uncertainty and variability in exposure assessment at the end of Chapter 8.

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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 in 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."

**EPA Response:** Figure 8-1 and associated text deleted.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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 then 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[s] that it is a common sense technique that involves probabilistic risk assessment and advanced modeling tools.

**EPA Response:** Text revised.

**Submitter:** Kenneth T. Bogen (Managing Scientist Exponent, Inc., Center for Occupational and Environmental Health Risk Assessment)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:**

Chapter 8 (“Uncertainty and Variability in Exposure Assessment”) of the peer review draft of the U.S. EPA 2015 Guidelines for Exposure Assessment appropriately reviews many of the same concepts that are addressed in Chapter 2 (“Variability and Uncertainty”) of the U.S. EPA Exposure Factors Handbook 2011 Edition (EPA/600/R-090/052F) (U.S. EPA 2011). However, compared with the draft Chapter 8, Chapter 2 of the Handbook better explains and documents (1) when and (mathematically) how both uncertainty and variability need to be considered jointly but distinctly in quantitative exposure and health risk assessment, and (2) ways that variability (per se) associated with individual exposures and risks directly affects uncertainty (per se) in estimated population risk. Thus, while the title of Chapter 8 clearly addresses both uncertainty and variability, the last of the six paragraphs that introduce Chapter 8 that appear just before Section 8.1 (Terminology) (the first five of which cite no references), lists references describing the history only of how “EPA consistently has addressed the need to characterize uncertainty in risk estimates” and how the International Programme on Chemical Safety (IPCS)/World Health Organization (WHO) has more recently emphasized “uncertainty evaluation.” While a few of the references cited directly and specifically address the issue of joint uncertainty and variability in exposure and health risk assessment (most notably, NRC 1994), notably absent in the set of references cited here in Chapter 8 are publications that first explored and later reviewed this specific topic and applications of it in depth and in mathematical detail, including discussions of how it affects and is affected by decision-making context (Bogen 1986, 1990, 1995, 2005; Bogen and Spear 1987; Bogen et al. 2007; Bogen and Gouveia 2008). Some of these publications, and later ones also addressing this topic, were cited in the National Research Council Science and Judgment report (NRC 1994) that addressed uncertainty and variability and their joint analysis in detail, and were cited in Chapter 2 of U.S. EPA (2011) among suggestions for “further reading on variability and uncertainty.”

Importantly, Chapter 2 of U.S. EPA (2011) introduced the topic of uncertainty and variability in exposure assessment in a way that initially introduces the reader to how uncertainty and variability are distinct, but (and more clearly than Chapter 8) does so in a way that “motivates” (i.e., explains the purpose of) this distinction. Thus, Chapter 2 of U.S. EPA (2011) explains that Accounting for variability and uncertainty is fundamental to exposure assessment and risk analysis... Given that exposure and susceptibility to exposure is usually not uniform across a population, accounting for variability is the means by which a risk assessor properly accounts for risk to the population as a whole... [where] variability arises from heterogeneity across people, places, or time, [and] uncertainty [reflects] a lack of knowledge about factors affecting exposure or risk... [T]he U.S. EPA (1995), following the NRC (1994) recommendation, has advised the risk assessor to distinguish between variability and uncertainty.

Likewise, although (without explicit acknowledgement) the proposed Chapter 8 adopts the key recommendation made by NRC (1994) and previously by others (e.g., Bogen and Spear 1987), that assessors distinguish between variability and uncertainty as these characteristics pertain to inputs of exposure and risk

assessment, readers would benefit from at least a brief explanation of its mathematical rationale and practical utility, specifically in relation to different types of exposure and risk estimates that assessors may need to generate. For example, such an explanation might start by posing an example in which—contrary to the recommendation—no distinction was made at all between variability and uncertainty, as these characteristics pertain to all statistically modeled assessment inputs. Assessment outputs obtained in this way could be used only for the restricted purpose of characterizing exposure or risk to an individual drawn at random from a modeled population at risk (Bogen and Spear 1987; Bogen 1990). While such outputs would be highly relevant to decisions that focus a single individual involved in civil litigation, for example, rarely if ever would they be relevant to assessments intended to support either protective or predictive regulatory goals (Bogen et al. 2009).

Protective regulatory goals typically (depending on governing statutes) require assessing exposure and risk to individuals that are relatively highly exposed and/or at upper-bound levels of risk, in a way that accounts conservatively for uncertainties in the inputs to the assessment, whereas predictive regulatory goals typically require best estimates that support objective comparisons of exposure or risk when trade-off or resource- allocation decisions are required to minimize the public health consequences of exposure or risk (Bogen 2005; Bogen et al. 2009).

EPA has many statutory responsibilities that require protective assessments, but the Agency also has statutory responsibilities that require predictive-type assessments of the total number of people predicted to be harmed due to specified environmental exposures, and additionally has some flexibility to allocate resources in ways that presumably are intended to minimize exposures and associated predicted harm in a way that balances cost- effectiveness and fairness (NRC 1994; Bogen et al. 2009; Bogen 2014).

Protective assessments, by definition, require analysis of joint uncertainty and variability, to ensure that an adequate (statutorily defined or implied) level of protection or safety is attained in both the uncertainty and variability dimensions of estimated exposure or risk. Predictive assessments must also carefully distinguish uncertainty from variability as they pertain to assessment inputs, but in this case, for the ultimate purpose of estimating one or more (e.g., exposure-specific) population risks (i.e., the number of cases anticipated in an exposed population), and their associated levels of uncertainty, so that these can be reported or compared meaningfully (Bogen 2005). The expected number of cases requires conditioning an assessment on the arithmetic mean value of each assessment input, only among the set (V) of such inputs that each contribute only into inter-individual variability per se in estimated risk (irrespective of uncertainty), and uncertainty in risk (RV) calculated in this manner typically has an approximate Poisson-binomial (or nearly Poisson) distribution that is completely determined only by the estimated expression for RV, including its associated uncertainty (Bogen 1986, 1990; Bogen and Spear 1987). Note that “variability” reflected in each member of each such set V of input variables mentioned above typically does not include temporal or intra-individual variability, whenever such variability does not actually contribute to inter-individual heterogeneity in levels of risk experienced in a population at risk.

Thus, although toxic potency or climatic conditions may vary over age or over time, which may be important for some characterizations of risk (and hence, exposure), such sources of variability “disappear” once they are incorporated into calculations of acute or lifetime risk anticipated for each individual in an exposed population using a specific dose-response model. For example, dose-response models that assume damage proportional to cumulative exposure are sensitive only to the time- weighted average value of exposure and dose, and are not affected by day- today or year-to-year fluctuations in factors contributing to exposure or dose. Other models may be sensitive to peak values of exposure and effective tissue concentrations. Consequently, the very definition of (relevant) “variability” in an exposure or risk assessment can depend both on dose-response models applied in or relevant to, and on the explicit purpose(s) of, an exposure or risk assessment. Chapter 8 readers might benefit from citations to more detailed discussions addressing these concepts (Bogen 1990, 1995, 2005, 2014; Bogen and Spear 1987; Bogen et al. 2009; NRC 1994 [Appendix I]).

**EPA Response:** Chapter 8 addresses the importance of considering and communicating uncertainty and variability when conducting exposure assessments. Appropriate references that support the topic are included throughout the chapter.

**Submitter:** Kenneth Unice, M.S. (Science Advisor, Cardno ChemRisk)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** Chapter 8: This chapter on uncertainty and variability presents an opportunity to incorporate an explanation of “conservatism” in EPA assessments, as discussed in the staff paper. An important concept that is not adequately conveyed in the draft guidelines is that exposure or dose cannot be determined with absolute certainty, thus EPA assessments prefer an approach that should not underestimate exposure (and risk) taking into account data gaps, uncertainty and variability. The staff paper notes:

“Because of data gaps, as well as uncertainty and variability in the available data, risk cannot be known with absolute certainty.”

“In other words, EPA seeks to adequately protect public and environmental health by ensuring that risk is not likely to be underestimated.”

Over time, many stakeholder concerns have focused on how “adequate protection” is defined, which is addressed as part of the risk assessment, risk management policy and process. There is no universal policy, process or rule that will eliminate this concern in future assessments because exposure (and risk) cannot be known with absolute certainty, and societal views on acceptable risk are dynamic across several dimensions,. Therefore, it is recommended that this document advance the discussion on conservatism and concisely explain how the principle of transparency, and processes of peer review, stakeholder engagement, and interaction between risk managers and risk assessors work together to define and ensure “adequate protection” in the presence of uncertainty, variability and data



gaps. It is important to communicate that the agency embraces peer review and stakeholder engagement as important “checks and balances” on the definition of “adequate protection” and “conservatism” in all risk assessment activities.

**EPA Response:** Text revised.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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 err 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, Bayesian 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.

**EPA Response:** Text revised.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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 conservatism/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.

**EPA Response:** Text not revised because the level of detail on distinguishing between uncertainty and variability requested by this commenter is beyond the scope of this document. References have been added where readers can find greater detail on uncertainty and variability. The definition of sensitivity analysis in Box 8-1 has been revised to describe the reason for any sensitivity analysis more clearly and to better describe how a sensitivity analysis is generally done (following the PRA White Paper, page 40). The definition of decision uncertainty and associated discussion have been modified for clarity.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the commenter does not provide specific recommendations for revisions.

  

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because this chapter reemphasizes the importance of planning and scoping and problem formulation and communication with stakeholders. More details and examples can be found in the included references. Text was revised to provide references and links to previous chapters and to include references to PRA methodology.

  

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

  

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Page 141, paragraph 3: I would suggest revising the first sentence to read “EPA has acknowledged 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Figure 8-1 deleted.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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

**EPA Response:** Text not revised because Section 8.2.1 emphasizes the importance of communication throughout, starting in the Planning and Scoping for Characterizing Uncertainty and Variability discussion, while emphasizing the importance of communication between assessors and risk managers/decision makers early in the process (e.g., planning, scoping and problem formulation). The text also emphasizes the importance of communicating with stakeholders.

Text revised in Section 9.4.

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**Location: Chapter 8, Page 140, 1st paragraph**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Fifth sentence: not all of these are discussed in section 5.5 as stated  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 140, 1st paragraph, lines 4-5**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Delete the sentence in these two lines. It is redundant.  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 140, 1st paragraph, lines 9-11**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** This sentence repeats other content in paragraphs 1 and 2.  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 140, 2nd paragraph, lines 10-12**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 140, last paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** I suggest removing the hyphens from risk management and decision making.

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 141, 2nd paragraph after bullets**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 141, 4th paragraph, line 1; 6th paragraph, line 1**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Flip the “for” and “both.”  
Replace “This” with “These.”

**EPA Response:** Text revised with deletion of sentence including the text identified.  
Text not revised from “This” to “These” because the term Guidelines is a collective noun and therefore takes a singular verb.

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**Location: Chapter 8, Page 141, Box 8-1**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** Bullet 1. I suggest using the 2nd to last sentence as the first sentence, and rewriting what is currently the first sentence.  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 141, Section 8.1, 1st paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** “the lack of, incomplete or incorrect information.” I found this awkward; the document should use parallel construction in lists.  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 141, Section 8.1, last paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** I had trouble parsing this list. Is it describing six types, or three, or two?  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 142, Box 8-1**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** I’m not sure what the authors mean by the “laws of mathematical statistics and of Monte Carlo analysis.”  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 142, end of page**

---

**Submitter:** Christopher W. Greene, M.S.



**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** This bullet seems “lost”—not near the others in the set.  
**EPA Response:** Text revised.

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**Location: Chapter 8, Page 143, Table 8-1**

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**Submitter:** Clifford P. Weisel, Ph.D.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** The example for Random Sampling Error is a poor choice and not very illustrative.  
**EPA Response:** Text revised.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** To clarify, revise to read “Use of a small sample of individuals to estimate risk to all exposed workers”  
**EPA Response:** Text revised.

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**Location: Chapter 8, Page 144, 1st bullet**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** It would be worth discussing here relationships between LOD and sensitivity.  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 144, Figure 8-1**

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**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** 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?

**EPA Response:** Figure 8-1 deleted.

---

**Location: Chapter 8, Page 145, 3rd paragraph, last line**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Change "this" to "these."

**EPA Response:** Text not revised here, or in other portions of the document, because "This" is the proper term. The agency has chosen to refer to *Guidelines for Human Exposure Assessment* in the singular reflecting its use as a collective noun.

---

**Location: Chapter 8, Page 145, Section 8.1.1**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 145, Section 8.1.3**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** The whole section discusses variability, but does not address the impact of such on uncertainty. Have I missed something?

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 145, Table 8-2**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** In row “Will using a combined dataset be a problem? The Question/Approach is not clear. What is “data of one type or another?”

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 146, Table 8-2**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “Will using a different dataset be a problem?” seems to be a better match for the question asked in the Questions/Approaches box

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 147, Section 8.2, 2nd paragraph**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** “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.

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 147-148, bullets**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** Ultimately, the content of these bullets is focused on regulatory decision making. This document could address other frameworks as well.

**EPA Response:** Text not revised; the bullets emphasize a general approach to address uncertainty and variability across EPA decisions, some of which are regulatory.

---

**Location: Chapter 8, Page 147-148, Section 8.2.1, list of questions**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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?
- Are the needed skills (e.g., statistical expertise) and experience available to perform the analysis?
- How will the uncertainty analysis be communicated to the risk managers/decision makers and stakeholders?

**EPA Response:** Text revised.

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**Location: Chapter 8, Page 148, 3rd bullet**

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**Submitter:** Christopher W. Greene, M.S.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** How is this different from the first bullet on the previous page?

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 148, bullets**

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**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** How will uncertainty analysis be communicated to community members?

**EPA Response:** Text not revised because Section 8.4 addresses communication of the results of the uncertainty and variability evaluation.

---

**Location: Chapter 8, Page 149, 1st bullet at bottom**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Tiered Approaches  
**Comment Type:** Peer Review  
**Comment:** Are input variables correlated? This can reduce the efficiency of collecting data, cf. temperature and ozone  
**EPA Response:** Text not revised; determinations regarding collection of other parameters are addressed in the development of data quality objectives discussed in Section 5.3.

---

**Location: Chapter 8, Page 149, 1st paragraph, line 8**

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**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 149, Section 8.2.3**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** This section might also refer the reader to the material in Section 8.4.  
**EPA Response:** Text revised.

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**Location: Chapter 8, Page 150, Figure 8-2**

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**Submitter:** Paloma Beamer, Ph.D.  
**Topic:** Uncertainty and Variability  
**Comment Type:** Peer Review  
**Comment:** This figure is too sophisticated. There need to be less use of acronyms and they need to be better defined within the text.  
**EPA Response:** Text not revised; the acronyms are defined in the figure and the figure is a graphic representation of the text.

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**Location: Chapter 8, Page 151, 5th paragraph**

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**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Tiered Approaches

**Comment Type:** Peer Review

**Comment:** 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:

$$\text{Var(Exp)} = \sum_i \sigma_i^2 \left( \frac{\partial \text{Exp}}{\partial X_i} \right)^2$$

Where i indexes variables and factors

**EPA Response:** Text not revised because a reference is provided for additional information.

---

**Location: Chapter 8, Page 152, Figure 8-3**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Tiered Approaches

**Comment Type:** Peer Review

**Comment:** Are the colored data meant to represent “real” measured data? Is the model used normal or lognormal?

**EPA Response:** Text not revised; Figure 8-3 is not in the document.

---

**Location: Chapter 8, Page 153, 3rd bullet**

---

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Comparing the estimated exposure to [toxicology-based] screening values

**EPA Response:** Text not revised because the bullet defines dose as reference doses, for example, and concentrations as soil concentrations, for example.

---

**Location: Chapter 8, Page 153, 3rd-4th paragraphs**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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 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]"

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 153, Section 8.3.2, 1st paragraph**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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)."

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 154, 4th paragraph**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** What about correlation among variables?

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 157, 1st paragraph, lines 2-4**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

---

**Location: Chapter 8, Page 157, Section 8.4**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** Is this not the purview of Chapter 9?

**EPA Response:** Text not revised because this discussion is designed to emphasize the importance of considering communication of uncertainty and variability as part of this part of the assessment.

---

**Location: Chapter 8, Page 158, 1st paragraph, lines 11-12**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the reference is to Chapter 9 in this document.

---

**Location: Chapter 8, Section 8.1.2**

---

**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** Page 146, Table 8-2, 6th element. Use of term “attractiveness” seems odd.

**EPA Response:** Text revised.

---

**Location: Chapter 8, Section 8.2.1**

---

**Submitter:** American Chemistry Council (ACC)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** Page 148, bullet 6. EPA should revise the question as follows: “Assess availability of specific skills and experience (e.g., statistical expertise) needed to perform the analysis and if not available, consider how to obtain them.”

**EPA Response:** Text revised.

---

**Location: Chapter 8, Section 8.4**

---

**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial



**Comment Type:** Public

**Comment:** Section 8.4. There is a cross reference to Section 3.2.2 but it was unclear what that cross reference was. Is this a typo? Should it be 9.2.2?

**EPA Response:** Text not revised because Section 3.2.2 discusses the need to begin communicating the conceptual model with stakeholders.

## Chapter 9. Developing a Communication Plan and Presenting Results for Exposure Assessments

---

### Location: Chapter 9

---

**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.”

**EPA Response:** Text revised.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Michael A. Jayjock, Ph.D., CIH

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; Section 9.3.4 (formerly Section 9.3.5) includes discussion of communicating uncertainty.

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised in Box 9.1. It provides general resources and guidance on community involvement and communication, which is consistent with the section title and content of an “Overview.”

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Communication

**Comment Type:** Peer Review

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

**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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).

**EPA Response:** Title and text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised to reflect a dialogue rather than a one-way discussion.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised throughout the document on communication. Content was added in Chapter 3 to include a discussion with stakeholders at the outset and the language reflects more of dialogue than one-way discourse.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Communication

**Comment Type:** Peer Review

<b>Comment:</b>	<p>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.</p> <p>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.</p> <p>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 SEAOS 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.</p> <p>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.</p>
<b>EPA Response:</b>	Title revised; links to Chapter 7 revised; Box 9-1 updated.
<b>Submitter:</b>	The Teratology Society
<b>Topic:</b>	Communication
<b>Comment Type:</b>	Public
<b>Comment:</b>	<p>Chapter 9, Presenting and Communicating Results mentions the various audiences for an exposure assessment on page 164. Among the potential audiences is a mention of the scientific community. Should there be a more specific mention of health care professionals and Teratogen Information Service organizations that could provide guidance for reproductive health? A similar question applies for Section 9.4 on page 166 – where would health care professionals/hotlines fit in?</p>

Table 9-1 (page 167) summarizes General Considerations for Good Risk Communication. “Good Communication” lists, among others, “Use credible sources: government agencies, scientific experts and reliable news sources (Associated Press, Reuters, etc.)”, while “Poor Communication” lists “Use [of] noncredible sources: lobbying groups or industries.” This approach is naïve. The key item is that the source of scientific information should be credible and scientific, based on evidence, and that includes data collected by various scientists – all of which should be able to stand up to peer scrutiny if not undergoing a formal peer-review. This could be reworded to: for good communication, “Use credible sources: scientific studies, directly available or reported through reliable sources” and for poor communication, “Use noncredible sources: nonscientific sources or claims unsubstantiated by evidence.”

**EPA Response:** Text and Table 9-1 revised.

---

**Location: Chapter 9, Page 159, 4th paragraph**

---

**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** This has been discussed in other Chapters  
**EPA Response:** Text revised.

---

**Location: Chapter 9, Page 159, Section 9.1**

---

**Submitter:** Rebecca T. Parkin, Ph.D., MPH  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** The title of this section is too broad for the content indicated by the title of the chapter.  
**EPA Response:** Title revised.

---

**Location: Chapter 9, Page 160, Section 9.2.1**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** End of first paragraph: the list doesn’t use parallel construction (noun, noun, verb.)  
**EPA Response:** Text revised.

---

**Location: Chapter 9, Page 161, last line**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** Clarify this bullet. “appropriate for the intended exposure characterization.” Does this mean appropriate for the intended audience?

**EPA Response:** Text not revised; the bullet addresses characterization and not the level of presentation.

---

**Location: Chapter 9, Page 161, whole page**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** I thought this page was well-organized; presents principles, then elements of an exposure characterization.

**EPA Response:** Text not revised; as the commenter is complimenting the writing team.

---

**Location: Chapter 9, Page 162, Box 9-1**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** I think this Box is misplaced here.

**EPA Response:** Box 9-1 moved to Section 9.1.

---

**Location: Chapter 9, Page 163, 4th paragraph**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** These are important examples (in Risk Characterization Handbook) but the Handbook is 16 years old.

**EPA Response:** Text not revised because an update to the Risk Characterization Handbook is not available.



---

**Location: Chapter 9, Page 163, Section 9.2.3, 2nd paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “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.

**EPA Response:** Text not revised because this document discusses the importance of planning and scoping and problem formulation in Chapter 3, including coordination with the group overseeing the development of the assessment.

---

**Location: Chapter 9, Page 164, 4th paragraph**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** “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.

**EPA Response:** Text revised, including text boxes, tables and graphics.

---

**Location: Chapter 9, Page 164, paragraph 2ff**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised. The narrative is intended to indicate that the presentation of information depends on the recipient. Presentation of numerical values might better suit someone who wants to reanalyze the data, while graphics might be better suited to a visually attuned reader.

---

**Location: Chapter 9, Page 165, 1st paragraph, lines 10-11**

---

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review  
**Comment:** “These Guidelines for Human Exposure Assessment are not intended.....”  
**EPA Response:** Text revised.

---

**Location: Chapter 9, Page 165, 3rd paragraph, line 3**

---

**Submitter:** Alan H. Stern, Dr. P.H., DABT  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** After, “...states and tribes” add, “, potentially responsible parties.”  
**EPA Response:** Text revised.

---

**Location: Chapter 9, Page 165, Section 9.3.1**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** 1st sentence: is this statement intended to apply specifically to communication with risk managers/decision makers, or all audiences?  
**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** Last sentence: nonscientific aspects. Would this include political aspects?  
What other aspects?  
**EPA Response:** Text revised.

---

**Location: Chapter 9, Page 165, Section 9.3.2, 2nd paragraph**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** Example at the end of the paragraph: How were these communicated, and how can this inform new exposure communication challenges?  
**EPA Response:** Text revised.

---

**Location: Chapter 9, Page 165-166, Media Discussion**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

---

**Location: Chapter 9, Page 166, 4th bullet**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** The first five words are in a different typeface than the rest of the document.

**EPA Response:** Formatting revised.

---

**Location: Chapter 9, Page 166, bullets**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised; text box replaced.

---

**Location: Chapter 9, Page 166, top**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** Public relations and press releases can be problematic.

**EPA Response:** Text revised. Section 9.3.3 has been deleted.

---

**Location: Chapter 9, Page 166ff, Section 9.4**

---

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised to include a more robust discussion of uncertainty.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** Perhaps something could be added here on providing information in languages other than English to audiences the might need it.  
**EPA Response:** Text not revised because the *Superfund Community Involvement Handbook* is included as a reference in this document. The Handbook provides detailed information on considering the needs of the community such as press releases, announcements and translations of presentations.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised because EPA's webpage is Section 508 compliant.

---

**Location: Chapter 9, Page 167, Table 9-1**

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**Submitter:** P. Barry Ryan, Ph.D.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** 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.

“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.

**EPA Response:** Table 9-1 deleted.

---

**Location: Chapter 9, Page 167, Table 9-1, 3rd row**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Table 9-1 deleted.

---

**Location: Chapter 9, Page 167, Table 9-1, 7th row**

---

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** “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.

**EPA Response:** Table 9-1 deleted.

---

**Location: Chapter 9, Page 168, 4th paragraph**

---

**Submitter:** P. Barry Ryan, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** The National Children’s Study did a great deal of work on risk communication and ethics. This should be explored and referenced.

**EPA Response:** Text not revised because Chapter 7 provides information on ethical considerations and the need for communication with stakeholders.

---

**Location: Chapter 9, Section 9.4**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Communication

**Comment Type:** Public

**Comment:** 3. Page 167, Table 9-1. As noted previously, this table is outdated and should be removed or edited. Industry data should not be considered a non-credible source of information.

**EPA Response:** Table 9-1 deleted.

**Submitter:** The Adhesive and Sealant Council (ASC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** ASC would recommend the removal of language in Table 9-1 which describes industries as n “non-credible sources.” While industry often does have a stake in the outcome of the analysis, there is no reason to characterize an industry scientists as inherently “non-credible.” Many industry scientists receive national and international recognition in the scientific community as well serve on government science boards and professional societies.

**EPA Response:** Text revised; Table 9-1 deleted.

## Front Matter

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**Location: Cover Page**

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**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** the year of publication is 2016, not 2015.

**EPA Response:** Text revised.

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**Location: Executive Summary**

---

**Submitter:** American Chemistry Council (ACC)

**Topic:** Editorial

**Comment Type:** Public

**Comment:** in the first paragraph, revise the next to last sentence to read: “The Agency needs to understand whether an agent might cause a health effect an adverse health effect and if so how exposure to the agent could be reduced.”

**EPA Response:** Text revised.

  

**Submitter:** The Teratology Society

**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** The Executive Summary (page xiv) mentions that Chapter 4 discusses lifestyles, noting that exposure assessors need to be aware of a variety of “unique population characteristics and sociodemographic factors that might increase exposure or predispose a lifestyle, vulnerable group or population to greater risk”. In addition to the factors listed, we suggest that diet should be included. It might be assumed that cultural characteristics may include diet.

However, nutritional factors are especially important from a developmental perspective (for example, the role of folic acid in preventing neural tube defects), and should be considered separately from sociodemographic factors when assessing risk.

**EPA Response:** The issue of diet is outside the scope of the document.

  

**Submitter:** The Teratology Society

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** The Executive Summary indicates that the document updates and supersedes the 1992 guidance but “does not, however, serve as a detailed instructional manual...” (p. xiii). It is good to have the scope of the guidance stated early in the document, but it should be clearly stated where such detailed instruction on exposure assessment can be found. While the draft guidance states that the focus is on the non-occupational environment, statistics from the Department of Labor indicated several years ago that more women are working when pregnant and working later into their pregnancies than in previous eras. Therefore, from the perspective of developmental health scientists, occupational exposure during pregnancy is a growing concern. If such information will not be included in this guidance, appropriate resources should be included to cover this gap.

**EPA Response:** Text not revised because occupational exposures are beyond the scope of this document.

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**Location: Executive Summary, Page xii, 2nd paragraph, lines 1-2; Page xiii, 2nd paragraph**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** “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.”

**EPA Response:** Text not revised; Guidelines is a singular, collective noun that takes a singular, verb and singular adjectives.

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**Location: Executive Summary, Page xii, 2nd paragraph, lines 5-6**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** “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.

**EPA Response:** Text revised.

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**Location: Executive Summary, Page xiv, 2nd paragraph, line 4**

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**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Aggregate and Cumulative Exposure Assessment

**Comment Type:** Peer Review

**Comment:** What is status of update of Cumulative Risk Assessment guidance? Might want to mention that it is underway, if it still is.

**EPA Response:** Text not revised; the development of cumulative risk guidance is not ready for release.



## Other Comments, Non-Location-Specific

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### Location: Non-specific

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**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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

**EPA Response:** Text not revised; the document is intended for exposure and risk assessors at all levels of experience and expertise, as discussed in Section 1.2. That this document will be used primarily by risk assessors, risk managers and risk communicators at EPA is anticipated.

**Submitter:** Alan H. Stern, Dr.P.H., DABT

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:**

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 than 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 detail 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.

**EPA Response:**

Text not revised because the document provides adequate links and references to assist the exposure assessor in using the document. In addition, hyperlinks are

provided within the document to facilitate location of additional information on specific topics and specific pointers to other chapters and sections of the document.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Data

**Comment Type:** Public

**Comment:** The Guidelines raise several issues that fall under this general heading, and ACC suggests areas for improvement below.

1) Models and Information:

a) *Additional Models and Updated Hyper-Links:* In addition to the models listed in the document, other useful exposure tools developed in the US and internationally (discussed elsewhere in these comments) would enhance the depth and breadth of this document. We also note that a substantial number of the hyper-links tested are no longer functional. Finally, we note that while all of the models and information referenced in the Guidelines are useful, for some topics there may be more recent data in addition to the reference material. For example, many of the international developments cited earlier may be useful additions. In some specific areas it may be useful to include additional more recent studies, such as in Table 6-2 (Wetmore et al., 2011, Wambaugh et al. 2014).<sup>15</sup>

b) *U.S. Centric:* As discussed elsewhere in these comments, there is little mention of major global advances in exposure assessment science, data and models in the Guidelines. While this may be by design, the global nature of chemical markets has required U.S. chemical manufacturers to learn and utilize these now tested and proven advanced methods. ACC urges EPA to incorporate discussion of these international advances in exposure assessment in these Guidelines.

The omission of the important models and databases developed (and under development) under Europe's REACH initiative is significant.<sup>16</sup> Discussions about the EU's advances in consumer exposure assessment, in particular, are also worth the Agency's consideration for inclusion in these Guidelines.<sup>17</sup> Canada's toxic substances review and principles developed under its Chemicals Management Plan (CMP),<sup>18</sup> particularly for consumer products, is another source of data, information and models that would be valuable for EPA to discuss in this document for users to consider.

c) *Need for More Balanced Discussion of Impact of Exposure Information in Risk Assessments:* Throughout the document there is a tendency to focus discussion (e.g., see page 2) on exposure information that suggests high potential for risk to humans. This document should also acknowledge that exposure information which suggests that there is very low potential for risk to humans also be considered if available. For example, exposure information employed in prioritization schemes (e.g. in the TSCA Work Plan Chemicals program within OPPT) drives EPA decisions about whether chemicals are

high priorities for assessments as well as low priorities for assessments. Screening level exposure assessments similarly will affect EPA decision-making about high and low potential for risk and the need (or not) for more refined exposure assessment. EPA should carefully review this document to ensure a balanced discussion of decisions that could result from the use of exposure information.

2) Data Quality: ACC believes that data quality and review are critical in exposure assessments. More specific comments follow:

- a) *Principles of Data Quality*: On page 64 of the Guidelines, EPA cites to data quality principles that refer to standards on Assessment Factors that EPA set in 2003. While this is a good, basic document on the topic, more specific guidance would be helpful to evaluate the quality of exposure information. For example, greater discussion of some of the data quality elements cited in WHO (2008) would be useful.<sup>19</sup>
- b) *Representativeness*: The Guidelines mention the representativeness of exposure factor data (see first bullet on page 87), but with little discussion of the “relevance” or “appropriateness” of the data, extrapolations, and assumptions used in exposure assessment. ACC believes that greater attention to this important consideration should be given. Appropriateness of data to an exposure assessment is a critical data quality element that contributes to the credibility of the exposure or associated risk assessment. Further information on appropriateness as a data quality consideration can be found in WHO (2008), and would be useful to include. The WHO document presents a contemporary, comprehensive discussion of the principles related to data and methodology quality for exposure assessment.
- c) *Level of Detection*: Chapter discusses generally what to do if a material of concern cannot be detected. The discussion provides very limited practical information, however, about how to address non-detects. The document should cite the 1992 Guidelines’ discussion in section 5.1.2.2.1, which describes in more detail the strengths and limitations of available approaches.
- d) *Default Assumptions*: On the subject of selecting exposure factors for use in exposure assessment, the Guidelines do a good job of describing the procedures for the collection of situation-specific data, such as activity patterns and intake rates. As a general rule, we prefer the development and application of situation-specific exposure factors instead of defaults, particularly if the application of defaults introduces sufficient uncertainty in the assessment as to limit its utility in decision-making. The Guidelines acknowledge this point as part of the discussion of uncertainty, stating:

“A change in one or more input parameters within the range supported by the data might lead to a different risk management decision. If so, an exposure assessor might consider spending additional time and resources (e.g., collection of additional data, additional data analyses, more advanced statistical analyses of data) to refine input parameters and reduce uncertainty.” (page 140)

The Guidelines also identify two key considerations when selecting exposure factors:

- 1) are the exposure factor data representative of the exposures being assessed; and
- 2) if default values are being used because of a lack of site-specific or situation-specific values, what are the bases for these defaults? (page 86) However, the document does not give adequate treatment to the question of when default assumptions are inadequate to develop credible estimates of human exposure. Instead, the Guidelines merely refer to the 2009 Science and Decisions document as a source of guidance on this topic. The Guidelines would be enhanced by providing some specific examples of acceptable types of information for different types of decisions. In addition, a summary discussion on the use of defaults in exposure assessment in lieu of site-specific or situation-specific data would also be helpful.
- 3) Data Communication: As a threshold matter, it is always important when communicating data to recognize the objective and proposed use of data and the context for their use. It is critically important to always state the limitations of the data, when applicable.

When these Guidelines discuss data representation, the draft suggests that “presentation of data in graphical formats might be helpful in showing locations of concentrations, outliers and other parameters.” While this is true, it is also important to accurately represent the data and the associated uncertainties. Too often, authors interpret “graphical format” to mean posting a myriad of individual data points on a map, or otherwise providing a data “dump,” instead of an analysis. ACC believes that an analysis was probably intended in the draft Guidelines. The notion of scientific communication needs to evolve from “depicting data” to “communicating knowledge and understanding.” Generally, decision-makers and stakeholders alike, who are trying to understand exposure and risk assessments, find comprehensible interpretations of the data much more useful than the data themselves. The Guidelines would benefit from acknowledging this point (on page 94).

The Guidelines provide some good recommendations on the subject of communicating the results of exposure assessments and the broader risk assessments in which they are contained. The discussion could be improved by including a better explanation of how to communicate the results of an exposure assessment to the public, to scientists and other decision makers, including how to explain what an exposure assessment does not address, as well as what additional steps will be taken to complete a risk assessment and how to work with risk assessors to explain the exposure assessment in their report. The classic risk communication literature of Covello and Sandman offer a number of overarching principles and practical day-to-day pointers to improve risk communication. (See pages 165-167.) This includes discussion of the differences in risk communication to the public when the risk is low as opposed to when the risk is imminent or severe, etc.

ACC calls EPA's attention to Table 9-1 General Guidelines for Risk Communication, on page 167 of the Guidelines. This table falls far short in conveying a generally accepted principle for risk communication – the use of credible sources. The table includes in its list of credible sources of information “government agencies,” but it identifies “industries” as an example of “non-credible sources.” This reference to “industries” is unacceptable, and reflects a bias which is unsupported by science, policy or practice, since industry provides a significant amount of the information and data upon which government risk assessments rely. This statement should be deleted.

As EPA is well aware, many industry scientists receive national and international recognition in the scientific community, as reflected by their service on such bodies as the National Academies' Board on Environmental Studies and Toxicology (National Academies) and the EPA SAB, and as members of professional societies such as the Society of Toxicology.<sup>20</sup> Moreover, many ACC member company scientists routinely represent their organizations in community settings, where they enjoy considerable credibility on scientific matters. The data and information they generate is clearly entitled to consideration in a risk assessment, particularly on a weight- of-the-evidence basis.

Table 9-1 was lifted from a U.S. EPA document from 2007, (cited in Chapter 10 References as U.S. EPA. (2007j). At a minimum, inclusion of this table in the Guidelines reveals EPA's lack of review of the 2007 document and is a stark example of the need for EPA to review more carefully all the documents, references, models, databases, etc. cited in the Guidelines to ensure they are up-to-date and reflect current science, information and practices. Table 9-1 should either be deleted in its entirety or EPA should revise its contents to exclude the reference to “industries,” and cite to other more appropriate risk communication resources.

Further, to improve the recommendation on credible sources of information on exposure assessment, the Guidelines should focus first on scientific experts in exposure assessment, with a secondary goal of using experts with specific expertise in the area being evaluated (e.g. dietary intakes, consumption rates, habits and practices, etc.), and, in the case of a localized issue such as a waste site, local knowledge of the situation. In addition, local public health officials, such as poison control physicians, can often contribute valuable context to the exposures being considered.

In summary, ACC urges EPA to review its models, information and references to ensure they represent the most up to date versions and perspectives; ensure a balanced discussion of decisions that could result from use of exposure information; include more specific guidance on data quality principles; provide greater discussion of the “relevance” of exposure data, extrapolations and assumptions used in exposure assessment; provide more practical information about how to address “non-detects”; provide a summary discussion of the use of defaults in exposure assessment; and delete Table 9-1 or its reference to “industries” and cite to more appropriate risk communication resources.

Footnotes:

- <sup>15</sup> Wetmore, Barbara A., John F. Wambaugh, Stephen S. Ferguson, Mark A. Sochaski, Daniel M. Rotroff, Kimberly Freeman, Harvey J. Clewell et al. "Integration of dosimetry, exposure and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences* (2011): kfr254.
- Wambaugh, John F., Anran Wang, Kathie L. Dionisio, Alicia Frame, Peter Egeghy, Richard Judson, and R. Woodrow Setzer. "High throughput heuristics for prioritizing human exposure to environmental chemicals." *Environmental science & technology* 48, no. 21 (2014): 12760-12767.
- <sup>16</sup> See, for example, ECHA's Chemical Safety Assessment and Reporting (CHESAR) tool at: <https://chesar.echa.europa.eu/>
- <sup>17</sup> See Appendix A (attached)
- <sup>18</sup> <http://www.chemicalsubstanceschimiques.gc.ca/plan/index-eng.php>
- <sup>19</sup> 2008 World Health Organization, IPCS Harmonization Project Document No. 6, ISBN 978 92 4 156376 5, Uncertainty and Data Quality in Exposure Assessment.
- <sup>20</sup> Barrow CS, Conrad JW. 2006. Assessing the Reliability and Credibility of Industry Science and Scientists. *Environ Health Perspect.* 114(2): 153-155.

**EPA Response:** Many of these comments are addressed under the specific sections of the document. Hyperlinks were updated. Revisions include references to appropriate international organization documents, links to documents, and revisions in text. Table 9-1 was removed from the document and Chapter 9 revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Tiered Approaches

**Comment Type:** Public

**Comment:** D. Tiered Approaches to Exposure Assessment

ACC is very supportive of the Guidelines' recognition of the value of tiered exposure assessments – from screening level assessments to more complex assessments. (Page 2). ACC appreciates the more specific discussion of considerations in tiered assessments on pages 14-15 and pages 24-29. In its discussion of tiered exposure assessment, the document also appropriately highlights the notion of “fit for purpose” assessments: “The type and purpose of an exposure assessment determine the data and information requirements.” (Page 2).

The Guidelines, however, include more discussion of “high-end” or complex exposure science (such as “planning and implementing an observational human exposure measurement study” and probabilistic risk assessment), than screening level exposure assessments used in tiered approaches. While complex exposure topics are very important to many risk assessments, they neither address the screening level exposure information EPA needs to prioritize chemicals for

assessment, nor the screening level exposure assessment issues that EPA is currently facing under its TSCA Work Plan program or anticipated to need to address once House and Senate passed legislation reforming the Toxic Substances Control Act is enacted.<sup>10</sup>

Further, the document provides only basic considerations for tiered exposure assessments and overly simplistic assumptions about the differences between screening level exposure assessments and the more complex exposure assessments (page 15) and risk assessment framework in which they operate. The document could benefit from a more in-depth discussion of some of the principles that should underpin a “tiered” approach to exposure assessment as well as citations to references that discuss such principles which could inform users of these Guidelines. This should include clear and consistent guidance on application and interpretation of screening level exposure evaluations.

In screening level evaluations, EPA’s methodologies may use worst-case or high-end assumptions. This approach is very conservative and consistent with a screening-level risk assessment where health protective assumptions are appropriately used for parameters employed in calculating exposures and hazards to assure that potential risks are not underestimated. Screening-level assessments such as these are not designed to provide true and accurate estimates of risk. When a screening-level assessment indicates an acceptable level of risk, the Agency has a high degree of confidence that the potential risks are much lower than the calculation and therefore the true risks are lower and/or perhaps non-existent. However, when a screening-level risk assessment indicates a potential concern for a health or environmental effect, this does not mean that the true risks are significant and warrant action.

Rather, it means that the risk evaluation should be refined using more realistic and accurate parameters in the methodologies to calculate risks. The outcome is then a refined risk assessment that more accurately quantifies actual risks. Under the Health and Environmental Sciences Institute’s (HESI) coordinated Risk Assessment in the 21st Century (Risk21) project, an open access review article was published in 2014 that discusses Risk21’s principles and framework for decision-making in human health risk assessment.<sup>11</sup> The article emphasizes that problem formulation for risk assessment should not be a hazard-driven process, but instead should start with exposure, focusing on exposure scenarios of greatest concern. The article suggests this approach would result in an early estimate of potential human exposure in relevant populations, including susceptible populations that would characterize the degree of specific toxicological data needs.<sup>12</sup>

A second principle promoted in the Risk21 framework is that additional data should be acquired “only if necessary and when they add value.”<sup>13</sup> A third major principle is one of flexibility, “such that a higher tier hazard assessment approach can be coupled with a lower tier exposure approach, and vice versa.”<sup>14</sup> Including the principles of a tiered approach to exposure assessment would improve the usefulness of the Guidelines considerably.

In conjunction with problem formulation and scoping of assessments, tiered assessment concepts allow EPA to apply limited resources (both animal and



dollars) in an efficient manner to enable EPA and the regulated community to perform exposure assessments to the point (prioritization vs. screening level vs. refined) where decision-making is sufficient. The draft document would benefit from more information on the principles that are critical to conducting screening level exposure assessments, as well as citations to important reference material (such as Risk21) concerning screening level assessments.

Footnotes:

<sup>10</sup> The U.S. House of Representatives passed H.R. 2576, the TSCA Modernization Action of 2015 in June 2015 and the U.S. Senate passed S. 697, the F.R. Lautenberg Chemical Safety for the 21st Century Act, in December 2015. In March 2016, the House and Senate began to reconcile the two bills.

<sup>11</sup> Pastoor TP, Bachman AN, Bell DR, Cohen SM, Dellarco M, Dewhurst IC, Doe JE, Doerrer NG, Embry MR, Hines RN, et al: A 21st century roadmap for human health risk assessment. *Critical Reviews in Toxicology* 2014, 44:1-5.  
<http://www.tandfonline.com/doi/full/10.3109/10408444.2014.931923>

<sup>12</sup> Ibid.

<sup>13</sup> Ibid.

<sup>14</sup> Ibid.

**EPA Response:** Text throughout the document, including the section on tiered approaches, has been revised to address specific comments from the peer-reviewers, the public, and tribal nations. Chapter 3 of the document emphasizes the importance of planning and scoping and problem formulation and ongoing communication between the assessor, risk manager and stakeholder to evaluate data and use the information to support decisions. It also includes information that helps the team determine whether a screening level or more advanced assessment might need to be used to address the purpose of the risk assessment. The document also emphasizes the importance of coordinating with appropriate program staff.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Planning and Scoping and Problem Formulation

**Comment Type:** Public

**Comment:** C. Problem Formulation

ACC appreciates the Guidelines' discussion of the importance of problem formulation in exposure assessment. Clear articulation of the problem (or question/hypothesis) to be answered by an exposure assessment improves understanding of the assessment's focus and the data/information needed for EPA to evaluate. The discussion of planning, scoping, and problem formulation for exposure assessments in Chapter 3 complements well EPA's 2015 Human Health Risk Assessment Framework to Inform Decision Making (HHRA Framework). Importantly, this chapter also incorporates the "fit for purpose" concept, which is critical to ensure that the assessment is designed in a manner that is focused on the

decisions it is meant to inform. The chapter correctly acknowledges that the most defensible assessments are those that are conducted with a clearly articulated goal(s) and well-defined questions.

This chapter encourages each program office to follow its standard operating procedures (SOP) when conducting assessments. This is a recommendation on which we cannot comment since we have not reviewed the SOP of each program when conducting risk or exposure assessments, except to encourage each program office to ensure that the SOPs utilized are commensurate with best practices.

Consistent with EPA's HHRA Framework, Chapter 3 emphasizes the importance of public, stakeholder, and community input, particularly concerning who might be impacted by the assessment and how the assessment might be used. Importantly, Chapter 3 defers to EPA's Peer Review Handbook, Fourth Edition, which details the practice of peer review at EPA. In addition, this chapter does a good job of describing what problem formulation is and why it is such an integral component of any exposure assessment planning, i.e., it identifies the population the assessment will focus on; it contains a conceptual model that presents the anticipated pathways of the agent from source to population of concern; and it presents an analysis plan that lays out the approach that will be used to conduct the assessment. ACC strongly supports Chapter 3's discussion of problem formulation in exposure assessment and the "fit for purpose" concept.

**EPA Response:** Text not revised; as stated, Chapter 3 is essential for explaining the importance of peer review, problem formulation and the HHRA framework in establishing the basis for the exposure assessment. The document also provides links to SOPs and related documents and recommends contact with appropriate program staff for additional guidance in conducting a risk assessment.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** II. General Comments on *Guideline* Discussions

A. Purpose and Scope:

The Guidelines make clear that its primary focus is on human exposure to chemicals under non-occupational scenarios. Its purpose is primarily to discuss general principles of exposure science and to suggest consideration of EPA's current practices of exposure assessment.

The Guidelines specifically state that it "does not serve as a detailed instructional guide or supplant specific exposure guidance in use by Agency programs" (Page 2). Rather, the Guidelines urge assessors to "consult with their programs for specific standard operating procedures or guidelines." (page xii). As a result, these Guidelines are, for the most part, purposefully not prescriptive.<sup>9</sup> The draft Guidelines present extensive information that may be considered when conducting human exposure assessments. Because these Guidelines do not provide specific

directions, examples or signals of “preferred” approaches, however, the discussion of what to consider can be confusing. Thus, it is not clear what actually constitutes EPA “guidance” in this draft. As discussed in more detail in sections II B-J and III below, there are several areas in the Guidelines that should be clarified.

Footnotes:

<sup>9</sup> See discussion below in Section III E. Chapter 3(4), however, challenging this general perspective.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** EXECUTIVE SUMMARY

The American Chemistry Council (ACC) appreciates EPA’s efforts to update its 1992 Guidelines for Exposure Assessment (U.S. EPA 1992(c) in its peer review draft entitled “Guidelines for Human Exposure Assessment” (*Guidelines*). ACC fully supports the *Guidelines*’ recognition of the important role of exposure assessment in characterizing risk. The *Guidelines* discuss important science concepts that underlie EPA’s current practices in exposure assessment and risk assessment. This discussion is vitally important to ensuring credibility, reliability, and consistency in risk-based regulation of chemicals across all of EPA’s program offices. We appreciate, in particular, that the *Guidelines* have highlighted certain critical topics such as the importance of problem formulation, data quality, and the utility of tiered and fit-for-purpose approaches to exposure assessment.

ACC recognizes the significant level of effort that has gone into the development of the draft Guidelines, in both its discussion of the scientific concepts of exposure assessment and its compilation of many useful resources for exposure assessment. These Guidelines do not provide the same level of detailed guidance for practitioners as the 1992 Guidelines, however. ACC encourages EPA to include clear guidance on how to consider and implement the concepts discussed in the draft Guidelines. Further, ACC urges EPA not to view these Guidelines as a wholesale update and replacement of the 1992 Guidelines, as EPA suggests in the document. Rather, EPA should make clear in these Guidelines its support of continued use of the 1992 Guidelines to provide more specific instructions on how to conduct exposure assessments. EPA should also reference the 1992 Guidelines where appropriate throughout the document.

ACC urges EPA to pay particular attention to the *Guidelines*’ discussion of lifestyles, vulnerable groups, and populations of concern in Chapter 4 to ensure this chapter remains appropriately focused on the science of exposure assessment.

These *Guidelines* should indeed “guide” future exposure assessments. To improve the usefulness of these *Guidelines* to the EPA program offices, as well as to the regulated community, ACC makes several recommendations:

- The document is extensive and so would benefit from a “road map” of the document highlighting what is in the *Guidelines*, what has changed from the 1992 Guidelines, and how the document should be used;
- The *Guidelines* suggest that many materials, concepts, models, etc. be “considered,” but without significant direction as to which are the most important. EPA should clearly identify the “key considerations” for exposure assessments as part of this document;
- EPA should review carefully all the documents, references, models, databases, etc. cited to ensure they are in fact up-to-date and reflect current exposure science practices and information. In this same vein, EPA should review each chapter to fill in any missing, significant references, and check to ensure its many hyperlinks are operational;
- The Agency should delete Table 9-1 from the draft *Guidelines*;
- The Agency should provide more examples throughout the document; and
- EPA should update these *Guidelines* more frequently, e.g. every five years, or when a topical update is needed, in order to keep it current with new developments in both exposure and risk assessment.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Emerging Issues

**Comment Type:** Public

**Comment:** B. EPA Should Incorporate Important Emerging Exposure Topics in the *Guidelines*

The Guidelines’ discussion of several emerging exposure science areas or relevant topics is limited, in some cases intentionally (for example, on topics such as high throughput approaches, developments in personal monitoring/sensor analysis, meta-analysis, and nanomaterials). In particular, EPA notes that the Guidelines do not address how exposure will be integrated in the application of in-vitro methods (Tox/Risk21) for the range of chemical safety assessment needs (from chemical prioritization, test selection, hazard identification, margin of exposure, and ultimately, risk assessment).

ACC believes that the evolution of predictive toxicology around in-vitro methods is moving so rapidly that the role of exposure must be addressed in this document. We recommend that the final version of the Guidelines include at least a limited discussion of emerging developments in exposure science to give practitioners a sense of what EPA thinks will be important in this field and help build awareness so that practitioners can begin to develop greater expertise in emerging areas of exposure assessment. In addition, EPA should provide topical updates as supplements to the Guidelines on an as needed basis. To start, ACC recommends that EPA begin by committing to a multi- stakeholder effort to develop guidance on how exposure information will be utilized in 21st century toxicology and risk

assessment. Expansion of the consideration of emerging exposure science in future documents would also be useful. Finally, EPA should consider updating these Guidelines on a more regular basis, perhaps every five years as the field is undergoing rapid advancement.

**EPA Response:** Text revised.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** ACC's Suggestions for Strengthening the Guidelines

**A. EPA Should Make the Guidelines More Useful to Practitioners of Exposure Assessment**

The American Chemistry Council (ACC) appreciates EPA's efforts to update its 1992 Guidelines for Exposure Assessment (U.S. EPA 1992(c) in its peer review draft entitled "*Guidelines for Human Exposure Assessment*" (*Guidelines*). We fully support the *Guidelines*' recognition of the important role of exposure assessment in characterizing risk. Providing a compilation and discussion of the scientific concepts behind EPA's current practices of exposure assessment and risk assessment is vitally important to ensuring credibility, reliability, and consistency in risk-based regulation of chemicals across all of EPA's program offices. We appreciate, in particular, the discussion of the importance of problem formulation, data quality, and the utility of tiered and fit-for-purpose assessments.

The *Guidelines* generally read more like a reference resource or compendium of useful documents and concepts about the science of human exposure, rather than hands-on "guidance." Throughout the *Guidelines*, there are many suggestions to "consider" certain materials, concepts, models, etc. Because this is guidance, these suggestions are appropriately not prescriptive. The *Guidelines* provide limited guidance to practitioners, however, regarding "how" to incorporate these concepts, documents, and information, etc. into exposure assessments. This is in contrast to the 1992 Guidelines which contain much more detailed guidance that is very useful for conducting an exposure assessment.

Unfortunately, EPA indicates (at Section 1.2 on page 1) that these *Guidelines* supersede the 1992 Guidelines. To improve the usefulness of this document, we recommend that EPA not characterize these Guidelines as a replacement to the 1992 Guidelines, but rather cite to the 1992 Guidelines as a source of relevant information, as appropriate throughout the Guidelines. The *Guidelines* could also benefit from a "road map" of how to use the document, including in conjunction with the 1992 Guidelines. This "road map" might also be used to more clearly indicate where the Agency's views have changed since the 1992 Guidelines and to flag the *Guidelines*' new areas of focus.

To further improve the usefulness of these Guidelines, it's highly recommended that EPA more clearly identify the most significant considerations in exposure

assessment in the document itself. As it stands, the draft *Guidelines* are a comprehensive discussion and reference document that makes few judgments about which of its many recommended considerations are most important in exposure assessment. We think the document's usefulness would be greatly improved if EPA highlighted at the end of each chapter the "key considerations" from each chapter of the document. Such highlights might include concise, explanatory narratives about each key consideration. These could serve as a practical tool for practitioners to quickly ascertain whether, how and why they considered these key considerations, enabling them to better review, discuss, document and/or refine their exposure assessments as needed.<sup>1</sup>

Another suggestion is for EPA to ensure its Guidelines are truly up-to-date. ACC has identified some examples of discussion topics (e.g., consumer product exposure; far field exposure; data quality) in which more up to date references are lacking and has suggested including some references for the Agency's consideration.<sup>2</sup> ACC has also identified a table (Table 9-1) lifted from a 2007 EPA document that includes a statement that reflects an unacceptable bias against industry. This table should be deleted from the document. EPA should review its references, models, databases and information that it urges exposure assessors to consider to ensure they actually represent current thinking and practices.

Finally, ACC recommends that in the final version of these Guidelines EPA make an effort to include more illustrative examples throughout the document, particularly in its discussions of "newer" topics such as cumulative exposure, vulnerable populations, and biomonitoring.

Footnotes:

<sup>1</sup> For an example of how EPA might approach this recommendation, see Fenner-Crisp PA, Dellarco VL. Key Elements for Judging the Quality of a Risk Assessment. Environ Health Perspect. 2016 Feb 5. available at: <http://ehp.niehs.nih.gov/15-10483/>

<sup>2</sup> See Appendix A (attached)

**EPA Response:** Text revised and references and links updated, where practicable.  
Text not revised to expand the inclusion of numerous examples. EPA has provided illustrative examples or references to examples, but providing examples for all scenarios, methods, practices, etc., would significantly increase the length of the document. The range of exposure scenarios that EPA assessors experience makes inclusion of numerous examples impractical.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Peer Review

**Comment Type:** Public

**Comment:** EPA Should Allow Opportunity for Public Input on the Charge Questions to the Peer Review Panel

We urge EPA to release a draft of the charge questions before the peer review panel begins its work on the Guidelines. EPA's Scientific Advisory Board (SAB) has recognized the important role that the charge to the peer reviewers can play in evaluating Agency documents. Indeed, SAB reviews always now begin with a discussion of any needed changes to the charge document. These discussions have always included public input. Public input to the charge will help ensure a robust review that addresses concerns not only of EPA but also of the broader stakeholder community. ACC strongly recommends EPA release the charge questions in advance of its peer review of these Guidelines to ensure public input and a robust peer review.

**EPA Response:** Text not revised; the Guidelines is identified as "Other" by the Office of the Science Advisor consistent with *Peer Review Handbook, 4th Edition* (Handbook). Page 86 of the Handbook indicates there is no requirement to release peer review charge questions for public input. Nonetheless, the charge questions provided by EPA are broad enough to allow a wide range of comments on the overall content of this document.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Aggregate and Cumulative Exposure Assessment

**Comment Type:** Public

**Comment:** H. Aggregate and Cumulative Exposure Assessment

Aggregate and cumulative exposure assessment is mentioned on page 16 of the Guidelines and also intermittently throughout chapter 4. A detailed discussion of the key points related to cumulative and aggregate exposure, however, is not included in the document. Given the data and resource intensive nature of these types of assessments, it would be useful to include some discussion on the amount and type of data needed to provide realistic quantitative estimates as well as recent advances in approaches for assessing when this level of assessment should be undertaken.

Importantly, EPA should recognize that aggregate and cumulative assessments are not the "norm," but rather should be triggered by certain criteria. For example, both aggregate and cumulative exposure assessments represent complex higher tier assessments that require detailed data and understanding of exposure drivers and correlations between exposure parameters to develop useful quantitative estimates. Aggregate assessment requires a knowledge of all exposure sources for the agent under review, the quantity and frequency of contact associated with source, and the correlations between contact patterns for each source. Cumulative assessment compounds this complexity as it requires knowledge of which agents (among all possible exposure possibilities) to consider together, the aggregate exposure data needs for each agent, the correlations between co-exposure patterns for the different agents, and metabolic kinetics and interactions. Recognition of this complexity has led to a focus on tiered and iterative assessments, including screening approaches, that provide sufficient information to indicate that an aggregate or cumulative assessment would not be a priority.<sup>21</sup> ACC recommends



EPA include more discussion in the Guidelines on the factors that would trigger an aggregate or cumulative exposure assessment, including the amount and type of data needed to provide realistic quantitative estimates, and a discussion of recent advances in approaches for assessing aggregate or cumulative exposure assessment.

Footnotes:

<sup>21</sup> Boobis et al 2011, Crit Rev Tox 41(5): 369-383; Boobis et al 2011, Example Case Study B of Meek et al 2011 Reg Tox and Pharm 60(2), Supplement 1: S1-S14; Meek et al., 2011 Reg Tox and Pharm 60(2), Supplement 1: S1-S14; Price and Han 2011, Int. J. Environ Res Public Health 8:2212-2225; WHO / OECD / HESI workshop report:

<http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono%282011%2910&doclanguage=en>; SCHER, SCCS, SCENIHR, Opinion on the Toxicity and Assessment of Chemical Mixtures, 2012

[http://ec.europa.eu/health/scientific\\_committees/environmental\\_risks/docs/scher\\_o\\_155.pdf](http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf)).

**EPA Response:** Text not revised; aggregate and cumulative exposures are considered in the planning and scoping and problem formulation portion of the assessment considering program-specific guidance. The document recommends the assessor coordinate with their specific program to locate specific programmatic guidance. Appropriate references to EPA's document, *Guidance on Cumulative Risk Assessment Part 1 – Planning and Scoping*, are provided in the Guidelines.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Peer Review

**Comment Type:** Public

**Comment:** Peer Review

ACC strongly urges EPA to release a draft of the charge questions before the peer review panel begins its work on the Guidelines to allow for public input on the charge questions and ensure a robust review that addresses the issues of both EPA and the broader stakeholder community. ACC's recommendation is consistent with the EPA's Scientific Advisory Board's (SAB) recognition of the important role that the charge to the peer review panel –and public input on that charge -- can play in evaluating Agency documents.

ACC believes EPA must also address who qualifies as a peer reviewer. A brief overview of some of the elements of EPA's Science and Technology Policy Council's Peer Review Handbook, 4th edition, October 2015, is presented in Section 3.1.4 on pages 31 and 32 of the Guidelines. This overview defines who qualifies as a peer reviewer: "qualified individuals or organizations that are independent of those who performed the work and are collectively equivalent in technical expertise to those who performed the original work (i.e. peers)." ACC believes that this definition does not fully reflect the description of the



qualifications discussed in Chapter 5 of EPA’s Peer Review Handbook, in particular, the qualifications pertaining to “expertise.” The opening sentence of Chapter 5 of the Handbook states, “[a]s part of the peer review process, the Agency (or the contractor managing the peer review) must select peer reviewers who have technical expertise in the subject matter that is needed to answer specific charge questions.”

Section 5.2.1 of the Handbook states further that “it also is important to include a broad enough spectrum of other related experts to consider wider dimensions of the issue(s).” This suggests that the Handbook does not specifically link the technical expertise of a reviewer to the “technical expertise of those who performed the original work being reviewed,” which indeed could be far too limiting. For example, businessmen or women who understand product formulation and time sensitive import/export dynamics may be the best experts to consider what chemicals were used in manufacturing consumer products. Other examples are expertise in age- dependent activity patterns, food sources and dietary profiles in unique communities that may be ethnically defined and seasonally dependent, challenging standard assumptions and/or data based on the “general” population. Experts in these topics may not have academic pedigrees equivalent to the EPA exposure assessor, but they would have greater insights into the accuracy and relevance of the assumptions, data and defaults used in the assessment under review. In effect, the shorthand definition of peer reviewer in the draft Guidelines would, if applied, tend to ignore potentially valuable review input. Peer reviewers should be charged with assessing the relevance, accuracy, completeness of the data, extrapolations and assumptions in an exposure assessment – consistent with their area of expertise. ACC recommends that the Guidelines quote these sections of the Peer Review Handbook to avoid creating limitations on access to needed expertise in exposure assessment.

<b>EPA Response:</b>	EPA provided a response to comment regarding the charge to questions above. Appropriate links and references to the <i>Peer Review Handbook, 4th Edition</i> , are provided in Section 3.1.4 of the Guidelines for the exposure assessor to use in assessments. Comparable information is provided in Chapter 5 regarding peer involvement and peer review.
<b>Submitter:</b>	American Chemistry Council (ACC)
<b>Topic:</b>	Lifestages, Vulnerable Groups and Populations of Concern (Part of Executive Summary)
<b>Comment Type:</b>	Public
<b>Comment:</b>	ACC urges EPA to pay particular attention to the Guidelines’ discussion of lifestages, vulnerable groups, and populations of concern in Chapter 4 to ensure this chapter remains appropriately focused on the science of exposure assessment.
<b>EPA Response:</b>	Text revised.
<b>Submitter:</b>	American Chemistry Council (ACC)

**Topic:** Emerging Issues – Comments provided in March 22, 2016 Attachment – Comments of the ACC (page 1).

**Comment Type:** Public

**Comment:** We recommend that EPA strengthen the Guidelines by addressing the following topics that are largely absent from the document:

Emerging exposure issues, such as high throughput approaches;

Important international advances in exposure assessment, in particular those new developments in the EU under REACH, in Canada under its Chemicals Management Plan, and in joint international work via the OECD;

The science concepts behind consumer exposure issues, as well as guidance for practitioners, because this is an area of growing interest and attention in the US and around the world.

**EPA Response:** High-throughput approaches were identified in Chapter 2 under emerging issues. Because of the level of effort to confirm that guidance developed outside the United States is consistent with EPA guidance (and terminology), references to international reports and projects are provided but limited in scope. Reference to consumer or occupational exposure scenarios are noted where content is provided (e.g., models, databases).

**Submitter:** American Chemistry Council (ACC)

**Topic:** Peer Review = Attachment to March 20, 2016 letter.

**Comment Type:** Public

**Comment:** Finally, ACC urges EPA to release a draft of the charge questions before the peer review panel begins its work on the Guidelines, to allow for public input on the charge questions and ensure a robust review that addresses the issues of both EPA and the broader stakeholder community.

**EPA Response:** Text not revised; the Guidelines are identified as “Other” by the Office of the Science Advisor consistent with *Peer Review Handbook, 4th Edition* (Handbook). Page 86 of the Handbook indicates no requirement to release peer review charge questions for public input. Nonetheless, the charge questions provided by EPA are broad enough to allow a wide range of comments on the overall content of this document.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Peer Review – Attachment to ACC letter 20, 2016

**Comment Type:** Public

**Comment:** In addition, EPA undoubtedly recognizes that when final this document will be highly influential. As such we anticipate that EPA has planned a robust and transparent peer review. In particular, consistent with EPA peer review standards

and current practices of the EPA Science Advisory Board, we look forward to 1) opportunities to suggest experts for your peer review panel, 2) opportunities to comment on the charge questions to ensure that the scope and questions for the review are appropriate and encompass issues of potential concern, and 3) opportunities to engage with the peer review panel, including providing comments on the draft peer review report(s).

**EPA Response:** Text not revised; the document was identified by EPA’s Office of the Science Advisor as category “Other.” The peer-review was conducted consistent with the *Peer Review Handbook, 4th Edition* recommendations for peer reviews in this category.

**Submitter:** American Chemistry Council (ACC)

**Topic:** Problem Formulation, Data Quality and Utility of tiered and fit-for purpose approaches to exposure assessment.

**Comment Type:** Public

**Comment:** The American Chemistry Council (ACC) appreciates EPA’s efforts to update its 1992 Guidelines for Exposure Assessment (U.S. EPA 1992(c) in its peer review draft entitled “Guidelines for Human Exposure Assessment” (Guidelines). ACC fully supports the Guidelines’ recognition of the important role of exposure assessment in characterizing risk. The Guidelines discuss important science concepts that underlie EPA’s current practices in exposure assessment and risk assessment. This discussion is vitally important to ensuring credibility, reliability, and consistency in risk-based regulation of chemicals across all of EPA’s program offices. We appreciate, in particular, that the Guidelines have highlighted certain critical topics such as the importance of problem formulation, data quality, and the utility of tiered and fit-for-purpose approaches to exposure assessment.

**EPA Response:** Text not revised because the comment acknowledges the technical panel who developed the document. EPA agrees with the commenter regarding the importance of problem formulation, data quality, utility of tiered and fit-for-purpose approaches in an exposure assessment.

**Submitter:** American Cleaning Institute (ACI)

**Topic:** Peer Review

**Comment Type:** Public

**Comment:** As part of the path-forward for the Guidelines, we believe it would be valuable for EPA to release a draft of the charge questions before the peer review panel begins its work on the Guidelines in order to solicit public feedback. EPA’s Scientific Advisory Board (SAB) has recognized the important role that the charge to the peer review can play in evaluating agency documents. Public input to the charge will help ensure a robust review that addresses concerns not only of EPA but also of the broader stakeholder community.

**EPA Response:** Text not revised; EPA’s Office of Science Advisor classified this document in the “Other” category consistent with *Peer Review Handbook, 4th Edition*. The Handbook, Page 86, states:

“6.2.7. When May the Public Provide Comment During the Peer Review?  
Whenever feasible, EPA offices should make drafts of work products categorized as ISI and HISAs available to the public for comment, as well as a draft peer review charge, at the same time they are submitted for peer review.”

**Submitter:** American Cleaning Institute (ACI)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** In the Notice of Availability for the Guidelines,<sup>5</sup> the agency notes that the present document is an update to the 1992 document Guidelines for Exposure Assessment. The Guidelines do not provide the same level of detailed guidance for practitioners as the 1992 Guidelines for Exposure Assessment.

Consequently, we ask that EPA not to view these Guidelines as a wholesale update and replacement of the 1992 document, as EPA suggests in the Guidelines. Rather, EPA should make clear in these Guidelines that its support the continued use of the 1992 Guidelines for Exposure Assessment and is providing more specific instructions on how to conduct exposure assessments. EPA should also reference the 1992 Guidelines for Exposure Assessment where appropriate throughout the present document. Likewise, given the passage of time and the speed of advancement of science since the 1992 guidance, we believe the agency should as a regular practice update the Guidance regularly, perhaps on five year intervals, in order to remain current and relevant.

Footnotes:

<sup>5</sup>81 FR 774 (January 7, 2016)

**EPA Response:** The updated Guidelines supersedes the 1992 Guidelines consistent with Risk Assessment Forum procedures.

**Submitter:** American Petroleum Institute (API)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** API supports EPA’s efforts in the Guidance to address concepts such as approaches to addressing uncertainty.

**EPA Response:** Text not revised; the commenter supports the text on uncertainty in this document.

**Submitter:** American Petroleum Institute (API)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** Given the considerable and varied information regarding human exposure assessments and the almost limitless potential situations in which human exposure assessments may be employed, it is understandable that EPA's draft Guidelines read more as a compendium of science concepts and exposure assessment techniques than as guidelines that can be strictly followed.

Because the Guidelines attempt to cover so much ground, EPA has adopted the approach of providing a compilation of considerations encountered in the practice of exposure assessment without providing actual guidance. There are some steps EPA could take to make the Guidelines more useful in practice, including providing a section in each chapter that identifies what EPA considers the "key considerations" for the topic being covered. Even with such changes, however, the Guidelines are unlikely to serve as stand-alone guidance for the human exposure assessment practitioner. Therefore, we recommend that EPA view this Guidelines not as a wholesale replacement, but as a supplement to the 1992 Guidelines and communicate this in the document.

**EPA Response:** Text revised.

**Submitter:** American Petroleum Institute (API)

**Topic:** Emerging Issues

**Comment Type:** Public

**Comment:** We encourage EPA to provide additional information on various emerging issues and techniques in human exposure assessment. These emerging issues include integrating exposure assessments with high throughput toxicology as well as in-vitro toxicology techniques, and topics such as personal monitoring/sensor analysis and meta-analysis, which the Guidance addresses but only in cursory fashion.

**EPA Response:** Text revised.

**Submitter:** American Petroleum Institute (API)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** Uncertainty and Variability. API is pleased that EPA has devoted a chapter to the discussion of both uncertainty and variability in exposure assessments (Chapter 8). In doing so, EPA has recognized a crucial aspect of exposure assessment in order to accurately determine risk. Using sensitivity analysis to characterize uncertainty can be a valuable tool, not only to refine exposure assessments but also to increase the transparency of the risk assessment process.

**EPA Response:** Text not revised; Chapter 8 includes a discussion of a tiered approach to evaluating uncertainty and variability in an exposure assessment.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Editorial  
**Comment Type:** Peer Review  
**Comment:** The document uses brackets [ ] inside parentheses ( ) when they are nested. This looks strange to me—I would just use parentheses.  
**EPA Response:** Text revised.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Principles of Exposure Science/Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised because Table 2-1 provides definitions of exposure duration and exposure frequency that are used in evaluation of long- and short-term exposures.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Aggregate and Cumulative Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised; relative source contribution is program specific and beyond the scope of this document.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Purpose and Scope  
**Comment Type:** Peer Review  
**Comment:** Occurrence and monitoring of chemicals in the environment is mentioned early in the document, but not fully developed in later chapters.  
**EPA Response:** Text not revised because Chapter 5 provides extensive discussion of data quality and sampling.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Planning and Scoping and Problem Formulation  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text not revised; determinations regarding additional sampling, phasing, and review procedures are typically discussed during the problem formulation step and the quality assurance process, including the development of Quality Assurance Project Plans that outline the sampling and review process.

**Submitter:** Christopher W. Greene, M.S.  
**Topic:** Communication  
**Comment Type:** Peer Review  
**Comment:** 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 vector-borne illnesses. I would like to see this addressed in the communication section in the Guidelines.

**EPA Response:** Text not revised because Chapters 3 and 9 discuss the need for ongoing communication throughout an exposure assessment.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Tiered Approaches

**Comment Type:** Peer Review

**Comment:** 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.)



**EPA Response:** Text not revised because the document emphasizes the importance of coordinating with programs for specific guidance.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised; see specific responses to comments on Chapter 4.

**Submitter:** Christopher W. Greene, M.S.

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** All chapters should start on an odd-numbered page so that they appear on the correct (right-hand) side when printed.

**EPA Response:** Text not revised; EPA wishes to minimize white space.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because Chapter 1 identifies the audience for this document.

**Submitter:** Clifford P. Weisel, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** CropLife America (CLA)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** CLA members believe that the new material included on planning and conducting observational human exposure measurement studies, as well as consideration of life stages and sensitive populations in exposure assessments, is particularly relevant and important given the use of such study outcomes in current risk analysis for pesticides and pesticide active ingredients. It is, however, somewhat concerning that EPA acknowledges information provided in this draft document is the most current science used in EPA exposure assessments, and that it incorporates information about EPA current policies. If the document is a draft of information intended for external and independent peer review, how is it that this draft approach is part of the EPA exposure assessments and policies currently used in risk assessment by the Agency?

**EPA Response:** Text revised to address comments received during the peer review and public comment period. The text also recommends coordinating with staff in the programs for specific guidance.

**Submitter:** DuPont

**Topic:** Tiered Approaches

**Comment Type:** Public

**Comment:** The Guidelines would benefit from a more in-depth discussion of some of the principles that underpin a “tiered” approach to exposure assessment, including a consideration of the conditions under which situation-specific exposure factors are to be applied.

**EPA Response:** Text revised.

  

**Submitter:** DuPont

**Topic:** Data

**Comment Type:** Public

**Comment:** EPA should acknowledge the advances in exposure assessment methods developed by other national/international agencies (e.g., EU, Canada, OECD), as a way to promote international harmonization in exposure assessment;

**EPA Response:** Text revised.

  

**Submitter:** DuPont

**Topic:** Data

**Comment Type:** Public

**Comment:** The Guidelines should include a discussion of how exposure information can and will be utilized in 21st century toxicology and risk assessment;

**EPA Response:** Text revised.

  

**Submitter:** DuPont

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** EPA should clarify that the Guidelines are not a wholesale replacement for the 1992 Exposure Assessment Guidelines, but rather are meant to augment them;

**EPA Response:** Text not revised because this document will supersede the 1992 version.

  

**Submitter:** DuPont

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** The Guidelines need a more thorough and contemporary discussion of the application of biomonitoring data in exposure assessment and risk assessment.

**EPA Response:** Text revised.

**Submitter:** Earthjustice (Darien De Lu)  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Public  
**Comment:** Please protect all of us -- esp. vulnerable groups like children, the elderly, those with special sensitivities, and those who live in areas with particular concentrations and combinations -- from complex exposures.  
**EPA Response:** Text not revised because EPA's regulatory programs are designed to address exposures. Further information is available at:  
[www.epa.gov/lawsregulations/regulations](http://www.epa.gov/lawsregulations/regulations).

**Submitter:** Earthjustice (Darien De Lu)  
**Topic:** Aggregate and Cumulative Exposure Assessment  
**Comment Type:** Public  
**Comment:** We all need the protection that only you can offer! Please draw up guidelines that  
    --address all known toxic chemicals  
    --protect us from the effects of combined exposures to toxic chemicals in air, water, soil, consumer products and pesticides  
    --take into account uncertainties -- not ignoring them because they are inconvenient!  
    --reckon with the full spectrum of exposures, starting before birth and including the effects of concentrations of toxins in breast milk and meat foods  
    --take into account the latest research, measurement tools, and other developments in our understanding of toxin effects  
Thank you for your work in protecting all people -- rich and poor, young and old -- from the modern risks of diverse toxic substances in our environment.  
**EPA Response:** Text not revised because EPA's guidance in the area of cumulative risk assessment is identified in the document.

**Submitter:** Earthjustice (Greg Wingard)  
**Topic:** Lifestyles, Vulnerable Groups and Populations of Concern  
**Comment Type:** Public  
**Comment:** EPA's current approach to risk marginalizes the reality of chemical toxicity. In particular by the failure to consider the particular risk people are exposed to by a chemical, or set of chemicals from a site in the matrix of their existing and total exposures. This ends up just being one more way that EPA has failed its mission to implement environmental justice, as those with the highest body burdens and risk are going to be people of color, and low income. EPA has started to address this risk in implementing a different fish consumption factor for Native Americans

versus the general population. In Region X, EPA called Washington State on their proposed cancer based standards, partially on this basis. EPA has yet though to take into account matters like a local populations far greater than normal exposure to diesel emissions when setting cancer related cleanup standards at sites. This is the case even when there is available data that has looked at the risk, such as the community in the Southpark and Georgetown area of Seattle, next to the Lower Duwamish River Superfund site. EPA acknowledges this problem in the implementation of the Clean Water Act through setting Total Maximum Daily Loads, when pollutants in water body segments exceed water quality standards. The TMDL requires that standards in NPDES permits be ratcheted back to bring the water body segment back into compliance. It is common sense that if you are already at or over a threshold there is no margin of safety for additional exposure. So all things being equal, applying the same standards at sites in an affluent community with relatively low pollution risk factors will not compare to the impacts of implementing those same standards in a community with much higher pollution risk factors. EPA needs to get much more serious about environmental justice.

**EPA Response:** Text not revised because discussion of specific program decisions is beyond the scope of this document.

**Submitter:** Earthjustice (Sally Jane Gellert)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Risk assessment is never perfect, but full consideration must be given not only to all sources, but also to the special vulnerabilities of young children and consequences of exposure in utero. With full information, pregnant women can take better precautions; mothers can protect their children. Municipalities will have better information to consider when siting schools and for zoning overall.

**EPA Response:** Text not revised because Chapter 4 addresses lifestages and populations of concern.

**Submitter:** Earthjustice (Sally Jane Gellert)

**Topic:** Aggregate and Cumulative Exposure Assessment

**Comment Type:** Public

**Comment:** Thank you for considering my comments. It is so important to look at cumulative environmental impacts, rather than looking at each pollution source in isolation. Polluting facilities do not operate in a vacuum, they add to the burden already affecting a community. Good health depends on a low level of pollutants; if all sources are not considered, then the true impact of toxic substances on public health is underestimated. Given the EPA's mission of protecting the public health, it is imperative that the best technology for assessing cumulative impacts be used.

**EPA Response:** Text not revised because references to the cumulative risk assessment guidance are cited in this document.

**Submitter:** Earthjustice (Sally Jane Gellert)

**Topic:** Data

**Comment Type:** Public

**Comment:** As scientists, EPA staff knows that incomplete knowledge is better than no knowledge at all, and that conclusions can still be drawn from incomplete data. Risks of chemicals that have not been fully assessed cannot simply be ignored or discounted. Noncarcinogenic effects, not only exposure that leads to cancer, must not be neglected. Current science shows us that there are some chemicals for which there is no safe level (e.g., lead, arsenic); EPA must be clear that exposure to such chemicals is never acceptable. Using outdated data harms real people; it is that simple. These fixes cannot wait; they are already overdue; do not leave this for the next administration; we have to act now.

**EPA Response:** Text not revised because this document states the need to coordinate with specific program offices.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** Regulatory Use: Finally, we believe that the Guidelines need to be clearer as to the relationship between the concepts laid out in that document and EPA's application of its regulatory authorities. If the Guidelines are intended to provide useful guidance to Agency scientists as to how they can assess risk, subject to particular requirements that are provided in specific statutes or regulations, that needs to be clearly stated. Otherwise, we fear that the concepts laid out in the Guidelines may be interpreted as requirements that must be followed. The Guidelines document is not a regulation, and applying it as such would not be proper.

**EPA Response:** Text not revised because this document states the need to coordinate with specific program offices.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Biomonitoring

**Comment Type:** Public

**Comment:** Biomonitoring and Causation: We commend EPA for its extensive discussion of biomonitoring data and its potential uses in assessing risk. However, it is important to acknowledge, in the final Guidelines, that data showing significant levels of various contaminants as present in a population does not prove that there is a causal relation between those contaminants and actual physical effects seen in that

population. More is needed before a cause-effect relationship can be documented and then used in risk assessment.

**EPA Response:** Text revised.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Vulnerability to Risk: The Draft Guidelines stress the need to protect those who are particularly vulnerable to certain effects, such that they are at increased risk of experiencing those effects. While that focus is certainly appropriate, it is also important that the Agency recognize that there are situations in which the risks presented are less than is generally the case.

**EPA Response:** Text not revised because Chapter 4 addresses vulnerability, and discussion of risk is beyond the scope of this document.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Communication

**Comment Type:** Public

**Comment:** Public Participation: The FWQC supports EPA's emphasis, in the Draft Guidelines, on the need to clearly explain risk assessment and management decisions to the general public and to affected stakeholders, in terms that they can understand. In particular, it is critical, as EPA recognizes, for regulatory agencies to set forth limitations on the data that they make publicly available, so all parties can consider and discuss what uses should – and should not – be made of those data, before regulatory processes move forward, rather than afterward.

**EPA Response:** Text revised.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Peer Review

**Comment Type:** Public

**Comment:** Peer Review Procedures: We believe that the Draft Guidelines place undue restrictions on the process for selecting peer reviewers. EPA requires that any individuals selected for a peer review panel must have qualifications that are equivalent to the people who conducted the study in the first place. The problem with that test is that it does not focus on the actual skills held by the potential peer reviewers. People who have extensive experience in a particular field, such as exposure modeling, may not have the same academic qualifications as the initial researchers, but may actually have more practical experience in doing the type of study that is being reviewed. The final Guidelines should allow for those kinds of

experts to be part of the peer review process, based on their possessing the right skills and experience for the job.

**EPA Response:** Text not revised because this document includes links to the *Peer Review Handbook, 4th Edition* that addresses the selection of peer reviewers.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** Exposure vs. Sensitivity: In discussing populations that need special protection, the Draft Guidelines discuss two separate concepts: increased exposure to contaminants, and increased sensitivity to those contaminants. EPA needs to clarify that those are two entirely distinct concepts. The fact that a particular population may have a high level of exposure to a contaminant does not necessarily mean that the same population has become uniquely sensitive to the presence of that contaminant.

**EPA Response:** Text revised.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Communication

**Comment Type:** Public

**Comment:** Communication and Credibility: The Draft Guidelines contain a very useful discussion of communication issues, which properly stresses the importance of careful, thorough and clear communication of risk information to the public and to stakeholders. However, we do have one concern with that discussion. EPA identifies government studies as “credible,” and identifies industry studies as “non-credible.”

We think that this labeling is a gross oversimplification that has no basis in fact. We understand that agencies, in assessing studies undertaken by industry, may feel that they need to ensure that the study has not been affected by any conflicts of interest. However, that does not make all industry studies non-credible. Moreover, it is certainly not the case that every government study is credible. The credibility of any study needs to be assessed carefully, on the merits of that particular study, and decisions on study credibility should not be based on assumptions and biases as to the entities who conducted the study or sponsored its development.

**EPA Response:** Text revised.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Purpose and Scope

**Comment Type:** Public



**Comment:** Occupational Risk: While the Draft Guidelines focus – appropriately – on nonoccupational risk, there are a number of studies referenced that reflect data on occupational risks. EPA should recognize that there are significant differences in these two types of risk and their associated policy choices, and should explain in the document how the occupational data relate directly to assessment of the nonoccupational risks that EPA generally addresses.

**EPA Response:** Text not revised because Chapter 1 indicates that occupational exposure is beyond the scope of the Guidelines.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Data

**Comment Type:** Public

**Comment:** Exposure and Current Uses: One factor that should be considered in assessing exposures is the extent to which the contaminants at issue are being used currently. If the chemicals are present in the environment due to past uses only, that is important to factor into the determination of how and to what extent humans will be exposed. This issue could use more attention in the Guidelines than is currently the case.

**EPA Response:** Text not revised because the document indicates the importance of coordinating with programs for specific guidance.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Data

**Comment Type:** Public

**Comment:** Non-Detect Values: The Draft Guidelines appropriately recognize that there are a number of options available for addressing non-detect values in data collected on human health risks. We believe that this discussion in the document can be expanded, to note the myriad statistical tools that can be used to deal with non-detects. Use of those tools is far superior to the use of simplistic, arbitrary assumptions that are not based on good science.

**EPA Response:** Text revised.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Uncertainty and Variability

**Comment Type:** Public

**Comment:** *Probabilistic Risk Assessment:* We support the Agency's decision to discuss probabilistic risk assessment (PRA) in detail in the Draft Guidelines, since it is an important tool for EPA and other stakeholders to utilize in assessing human health risks. While we have sometimes encountered reluctance on the part of Agency staff

to utilize PRA, the Draft Guidelines make clear that it can and should be used by EPA in appropriate situations. In fact, we think that the document could be strengthened in this area, by listing each of the numerous matters on which EPA has used PRA tools to guide the regulatory process and to make statistically robust policy decisions.

**EPA Response:** Text not revised because the 2014 PRA document is included in the references.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** *State Flexibility:* It is important to keep in mind that risk assessment and risk management decisions are made by different parties in different regulatory structures. Thus, while these decisions are made at the Federal level in programs under the Toxic Substances Control Act (TSCA), the structure is different under the Clean Water Act (CWA), where States have the authority to make these decisions, subject to Federal oversight. The Draft Guidelines lay out certain principles to be used in risk assessment, and EPA should make it clear that in programs where States can make decisions, the Guidelines cannot bind the States, and the State agencies have the ability to make their own decisions, based on factors important to them.

**EPA Response:** Text not revised because commenter recommends coordination with appropriate programs, which is already stated in the document.

**Submitter:** Federal Water Quality Coalition (FWQC)

**Topic:** Data

**Comment Type:** Public

**Comment:** *Exposure Ranges:* The Draft Guidelines pay significant attention to situations where exposure is high, and that is appropriate. However, the document should also recognize that there will also be situations where exposure levels will be low, and it should discuss how those circumstances should be addressed.

**EPA Response:** Text not revised because Chapter 5 provides definitions for several measures of exposure including reasonable maximum exposures, maximally exposed individual, and central tendency or average exposures. The document also recommends coordination with appropriate programs.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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).

**EPA Response:** The Guidelines emphasizes the general approaches to assessing exposures that are appropriate for both non-occupational and occupational exposure scenarios. Throughout the document, emphasis is placed on coordinating with the appropriate program for specific guidance.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because this is an area that needs further evaluation in an exposure assessment and is discussed in the planning sections of the document, for example, Sections 5.3.1, 5.3.2, 5.4.4 and 5.4.5.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Emerging Issues

<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	<ul style="list-style-type: none"> <li>•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.</li> </ul>
<b>EPA Response:</b>	Text revised.
<b>Submitter:</b>	Generally agreed upon by all reviewers
<b>Topic:</b>	Modeling
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	<p>The reviewers generally agreed that Chapter 6 does a good job explaining model selection. Some suggestions included:</p> <ul style="list-style-type: none"> <li>[1] Emphasize that a more complex model is not necessarily a better model.</li> <li>[2] Include a list of models.</li> <li>[3] Augment the geospatial model discussion.</li> <li>[4] Provide uniform level of details for each model.</li> <li>[5] Emphasize how modeling efforts and data collection can be used together.</li> </ul>
<b>EPA Response:</b>	<p>Responses to the suggestions follow.</p> <ol style="list-style-type: none"> <li>1. Text not revised; the current text indicates that model selection is dependent on the question(s) that need to be addressed. The current text indicates that model selection must begin with a conceptual model.  The text clearly indicates that more complex models might not be helpful and that model selection should be parsimonious and fit for purpose.</li> <li>2. and 4. Text not revised because maintenance of such a list is impractical for a document such as the Guidelines.</li> <li>3. Text revised to include geospatial models.</li> <li>4. Text not revised because Figure 6.3 addresses this issue.</li> </ol>
<b>Submitter:</b>	Generally agreed upon by all reviewers
<b>Topic:</b>	Planning and Scoping and Problem Formulation
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	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.
<b>EPA Response:</b>	Text not revised because Chapter 3 discusses the importance of planning and scoping and problem formulation and ongoing communication with stakeholders.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

**Comment:**

- 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.

**EPA Response:** Text not revised because references for more specific equations are provided in specific guidance documents included in the Guidelines.

  

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Biomonitoring

**Comment Type:** Peer Review

**Comment:**

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

**EPA Response:** Text revised.

  

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Principles of Exposure Science/Exposure Assessment

**Comment Type:** Peer Review

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

**EPA Response:** Text not revised because the approaches outlined in the document are generally applicable to individual chemicals and mixtures.

  

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Communication

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because this document focuses on the exposure component of a risk assessment.

Text revised to include a definition of “communication.”

Chapter 9 was extensively revised to include a more comprehensive discussion of community engagement.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** •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.

**EPA Response:** Text revised.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Modeling

**Comment Type:** Peer Review

**Comment:** •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.

**EPA Response:** Text not revised because the discussion of input parameters is outside of the scope of this document. The text indicates the importance of coordinating with specific programs for guidance.

**Submitter:** Generally agreed upon by all reviewers

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

<b>Comment:</b>	<ul style="list-style-type: none"> <li>•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.</li> <li>•A few reviewers thought the intended audience was unclear, in part because the level of detail varied too much throughout the document.</li> </ul>
<b>EPA Response:</b>	Text not revised because Chapter 1 identifies the intended audience for this document.
<b>Submitter:</b>	Generally agreed upon by all reviewers
<b>Topic:</b>	Planning and Scoping and Problem Formulation
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	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.
<b>EPA Response:</b>	Text not revised because exposure assessment is presented within the risk context.
<b>Submitter:</b>	Generally agreed upon by all reviewers
<b>Topic:</b>	Data
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	•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.
<b>EPA Response:</b>	Text not revised because data-sharing approaches are being developed and implemented across the Federal Government. Section 5.4 describes the new federal policy on making raw data available for research conducted with federal funding. It is beyond the scope of this document to provide a policy regarding access of raw data.
<b>Submitter:</b>	Generally agreed upon by all reviewers
<b>Topic:</b>	Aggregate and Cumulative Exposure Assessment
<b>Comment Type:</b>	Peer Review
<b>Comment:</b>	Some specific points emphasized, or additions suggested, by one or more reviewer include: Include a discussion on the determination of relative source contribution factors to ensure that aggregate exposure does not exceed health benchmarks.
<b>EPA Response:</b>	Relative source contribution is program specific and beyond the scope of this document.

**Submitter:** Michael A. Jayjock, Ph.D., CIH  
**Topic:** Aggregate and Cumulative Exposure Assessment  
**Comment Type:** Peer Review  
**Comment:** I agree with Mr. Greene that there should be some discussion about using exposure assessment to prioritize the risk from exposure to multiple chemicals.  
**EPA Response:** Text not revised because the evaluation of risk of exposure from chemical sources is a programmatic policy decision and outside the scope of this document.

**Submitter:** Michael A. Jayjock, Ph.D., CIH  
**Topic:** Purpose and Scope  
**Comment Type:** Peer Review  
**Comment:** 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.  
**EPA Response:** Text revised.

**Submitter:** Michael A. Jayjock, Ph.D., CIH  
**Topic:** Purpose and Scope  
**Comment Type:** Peer Review  
**Comment:** 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.  
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.  
**EPA Response:** Text revised to include summary bullets at the end of each chapter.  
Text not revised because illustrative examples or references to examples, where appropriate, are provided in the document. Providing examples for all scenarios, methods, practices, etc., would significantly increase the length of this document.



**Submitter:** Michael A. Jayjock, Ph.D., CIH  
**Topic:** Modeling  
**Comment Type:** Peer Review  
**Comment:** •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.  
**EPA Response:** Text revised.

**Submitter:** Nicole Cardello Deziel, Ph.D., MHS  
**Topic:** Emerging Issues  
**Comment Type:** Peer Review  
**Comment:** 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).  
**EPA Response:** Text revised.

**Submitter:** North American Metals Council (NAMC)  
**Topic:** Purpose and Scope  
**Comment Type:** Public  
**Comment:** In Section 1.2., Purpose and Scope of the Guidelines, the guidelines state that the updated document incorporates policy, methods, and data developed since the 1992 document, but does not specifically list the 2007 EPA Framework for Metals Risk Assessment as an information source for the update. EPA has recognized that metals present unique risk assessment issues and prepared the Framework for Metals Risk Assessment to address those unique attributes and behaviors when assessing risks. We urge EPA to incorporate the policies and methods from the Framework for Metals Risk Assessment into the updated human exposure assessment guidelines, or provide a specific citation to the Framework as the appropriate source for determining human exposure to metals and metal compounds.  
**EPA Response:** Text revised.

**Submitter:** North American Metals Council (NAMC)  
**Topic:** Data  
**Comment Type:** Public

**Comment:** NAMC requests that the guidelines give additional attention to background chemical concentrations from naturally occurring sources and how those should be addressed in a human exposure assessment. This issue is of particular interest for NAMC because mineral forms of metals are naturally occurring in the environment and as such, all environmental media will have naturally occurring mixtures of metals. These concepts are listed as key principles in the 2007 EPA Framework for Metals Risk Assessment and should be likewise highlighted in the updated EPA human exposure assessment guidelines.

**EPA Response:** Text revised.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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?

**EPA Response:** Text not revised because Chapter 1 identifies the audience for this document.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because this comment addresses toxicity, which is addressed in other documents developed by the Risk Assessment Forum and other parts of the agency. In addition, program-specific guidance might also address prioritization, for example, RAGS Part A (listed as a reference).

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Uncertainty and Variability

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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 be updated more regularly and be reflected in ExpoBox (<https://www.epa.gov/expobox>).

**EPA Response:** Text not revised because the text indicates this document supersedes the 1992 version and appropriate language from the 1992 Guidelines has been included in this update.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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).

**EPA Response:** Text not revised because Chapter 1 states that guidance on occupational exposures is not addressed in this document.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Data

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised as this document recognizes the iterative nature of an exposure assessment and the need to make a final decision based on the data. The determination regarding further sampling and analysis of data following action is a programmatic decision and, throughout the document, emphasis is placed on coordinating with appropriate program staff.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because Chapter 4 provides information on vulnerable populations and lifestages.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written document.

**Submitter:** Paloma Beamer, Ph.D.

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the document emphasizes the importance of planning and scoping and problem formulation where the issues raised in the comment would be considered. A significant addition to this document is the guidance addressing socioeconomic status of the potentially affected segment of the population. The action on how the programs address this is a risk issue and is outside the scope of this document.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised. EPA will consider next steps following publication of this document.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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;

- 1) 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?

**EPA Response:** Text not revised because this document provides the exposure assessor and others with information on how to approach and conduct an exposure assessment that meets the needs of the risk assessor, decision maker and stakeholders. The document provides links and references to specific guidance where additional information on specific topics can be found.

To limit the document to a more manageable size without substantially broadening the content and scope of an already large document, occupational exposures were not addressed because program-specific guidance is available.

The final review of this document will include another opportunity for review by programs within the Agency.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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 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.

**EPA Response:** Text not revised because the document identifies the range of users in the Executive Summary. The readership for this document has been revised per the reviewer’s comments. Comments from EPA’s interagency partners were incorporated prior to public comment and peer review. EPA has addressed comments from the public during this revision.

**Submitter:** Penelope A. Fenner-Crisp, Ph.D., DABT

**Topic:** Peer Review

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the document was sent to all program offices for review and comment. In addition, the document will undergo a final review before released in final form through the Science and Technical Policy Council, which includes all programs. Membership on the technical panels was open to experts from across the agency available to contribute their time and expertise. Nonetheless, programs who did not have staff available had opportunities to review and comment on the document. OPPT was provided an additional opportunity following the implementation of the Lautenberg Act (revised TSCA) to ensure this document is consistent with that statute.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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

**EPA Response:** Text not revised; no revision necessary because the commenter compliments the technical panel on a well-written chapter.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text not revised because the audience for this document is defined in the Executive Summary.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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 Guidelines. 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Editorial

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** Rebecca T. Parkin, Ph.D., MPH

**Topic:** Purpose and Scope

**Comment Type:** Peer Review

**Comment:** 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.

**EPA Response:** Text revised.

**Submitter:** The Adhesive and Sealant Council (ASC)

**Topic:** Tiered Approaches

**Comment Type:** Public

**Comment:** ASC applauds the Guidelines recognition of the value of a tiered approach to exposure assessments and the concept that the type and purpose of an exposure assessment should determine the data and the information requirements. However, there seems to be a much greater discussion of complex exposure science, such as “planning and implementing an observational human exposure measurement study” and problematic risk assessment than screening level assessment for tiered approaches. While not wanting to downplay the importance of these aspects of risk assessment, EPA would serve itself better if it were to address the screening level exposure information it will need to address its current TSCA Work Plan program or anticipated under the reforms of the Toxic Substance Control Act.

**EPA Response:** Text not revised because information is provided for both screening-level and complex assessments.

**Submitter:** The Adhesive and Sealant Council (ASC)

**Topic:** Data

**Comment Type:** Public

**Comment:** The Guidelines seem to concentrate on exposure work done in the United States. There has been significant work done with regard to exposure assessment in both

Canada and the European Union and a discussion of those efforts would strengthen the document as well as promote international; harmonization in this field of study.

**EPA Response:** Text not revised because the Guidelines emphasizes approaches that EPA uses in programs when developing exposure assessments; references to international guidance is included, as appropriate.

**Submitter:** The Adhesive and Sealant Council (ASC)

**Topic:** Data

**Comment Type:** Public

**Comment:** There has been increasing debate with regard to exposure to chemicals in consumer products as well as to products to which the public is exposed on daily basis (i.e. building construction materials). These are issues that ASC's members and other formulating manufacturers will continue to confront. While much work on good exposure assessment design for these type of products has been accomplished in recent years, the Guidelines provide only a limited discussion with regard to the topic. EPA should consider adding greater discussion of consumer exposure topics in the context of both the developments in the science of exposure assessment and specific guidance to practioners[practitioners].

**EPA Response:** Text revised and links updated.

**Submitter:** The Adhesive and Sealant Council (ASC)

**Topic:** Emerging Issues

**Comment Type:** Public

**Comment:** In addition, ASC believes there are other areas in which EPA should provide some additional discussion:

Exposure science is burgeoning area of study yet the Guideline's discussion of several emerging exposure science areas or relevant topics is somewhat limited (i.e. developments in personal monitoring/science analysis and nanomaterials). It would be helpful if in the final version of the Guideline, EPA included some discussion of emerging developments in exposure science to give practitioners a sense of what the Agency believes will be important in the coming years. Also this document represents the first update of this document in almost 25 years. Given the rapidly advancing work in the field, EPA should consider undertaking more regular updates of this document.

**EPA Response:** Text revised.

**Submitter:** The Adhesive and Sealant Council (ASC)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** ASC would like to point out that it has been noted that this new draft document does not provide the same level of detailed guidance for practioners[practitioners] as the Agency's 1992 Guidelines for Exposure Assessment. For that reason it is important that the Agency not consider this new document a complete replacement but instead allow the two documents to work in tandem. For example, EPA should make it clear in the new Guidelines its support for the continued use of the 1992 guidance document to provide more specific instructions on how to actually conduct exposure assessments.

**EPA Response:** Text not revised because this document supersedes the 1992 Guidelines, which is consistent with Risk Assessment Forum procedures.

**Submitter:** The Adhesive and Sealant Council (ASC)

**Topic:** Data

**Comment Type:** Public

**Comment:** ASC has been supportive of the Health and Environmental Sciences Institute's (HESI) Risk Assessment in the 21st Century (RISK21) project that is developing core principles and a framework for decision making in human health risk assessment. ASC would like to see EPA and industry involvement on how exposure data will be utilized in RISK21. ASC supports the inclusion of an exposure element rather than a hazard only approach with regard to risk assessment. ASC would encourage EPA to further support exposure scenarios of the finished formulated product (in our case finished goods) adhesives and sealants versus a CAS number only approach.

**EPA Response:** Text not revised because this document reflects current exposure assessment practices across the agency. It is not a review of the literature, nor does it capture other organizations' practices not used by EPA.

**Submitter:** The LifeLine Group

**Topic:** Peer Review

**Comment Type:** Public

**Comment:** Guidelines for Exposure Assessment emanating from the US EPA are worthy of a comprehensive peer review featured by the Science Advisory Board, Science Advisory Panel or by an outside science panel, operating with public meetings and paneled with global experts in the various exposure-related fields who have personal experience with data, monitoring, models and concepts now existing or evolving in the US, Canada, the EU, and elsewhere. The result could be a guideline that is comprehensive and serves as a useful tool for research, regulatory application, concepts for emerging challenges and foundation for existing and evolving models and approaches.

**EPA Response:** Text not revised. The document was peer reviewed by an independent panel consistent with the *Peer Review Handbook, 4th Edition*.

**Submitter:** The LifeLine Group  
**Topic:** Emerging Issues  
**Comment Type:** Public  
**Comment:** The Guidelines do not adequately address nano particle exposure and other contemporary challenges.  
**EPA Response:** Text revised.

**Submitter:** The LifeLine Group  
**Topic:** Purpose and Scope  
**Comment Type:** Public  
**Comment:** The Guidelines give sparse attention to the significant advances in exposure sciences promulgated by other countries or by US States (particularly California) or other US or foreign institutions, corporations, universities and researchers. Those omissions are significant and render the document inadequate as a guideline or even as a complete collection of concepts in the exposure sciences. The document is US centric and as such is a biased and is an incomplete discussion of contemporary human exposure assessment. If the US disagrees with exposure science concepts being developed, as with the extensive work in the EU or prioritization approaches adopted by California and Canada, it should at least acknowledge those significant bodies of work and explain EPA's disagreement with concepts, approaches, data base characteristics or other elements.  
**EPA Response:** Text revised, where appropriate, to provide references to international agency documents.

**Submitter:** The LifeLine Group  
**Topic:** Peer Review  
**Comment Type:** Public  
**Comment:** The Guidelines do not seem to reflect the practices or evolving concepts of all US EPA operating offices or regional offices in the development of human exposure assessment or application of those assessments. EPA has long been viewed as an active developer of the exposure sciences and its regulatory conclusions often rely heavily on applications of exposure sciences and exposure related data. As an EPA document, the Guidelines will be interpreted as a statement for all EPA assessments, notwithstanding the caveats of the Preface. All operating offices and regional offices of the Agency should review the document to assure the concepts, opinions, extrapolations and commentaries reflect their operating practices OR their exceptions should be clearly noted.  
**EPA Response:** Text not revised. The draft document was reviewed by Agency scientists, and the final version will be reviewed by Agency scientists before it is published.



**Submitter:** The Teratology Society

**Topic:** Lifestages, Vulnerable Groups and Populations of Concern

**Comment Type:** Public

**Comment:** In general, although fetal development and/or pregnancy are mentioned in a few places in the document [while not exhaustive, references to fetal development and/or pregnancy can be found on pages 7, 42, 43, 44, 45 and 47], we believe that the guideline could be improved by a fuller discussion of known or probable aspects of exposure that are unique to the embryo, fetus or nursing infant, as well as to the pregnant or nursing woman. For example, on page 43 the guideline states “Rather than considering children as a population group, the Agency has moved toward viewing childhood as a sequence of lifestages from conception through fetal development, infancy and adolescence.” However, in the tables and figures in this section, childhood age groups are shown starting from birth with no consideration for prenatal exposures. Additionally, we propose that where mentioned in the draft, “fetal exposures” be replaced by either “prenatal exposures” or “embryo/fetal exposures.” This is important because exposures during early embryonic development may have very different consequences compared to the same exposures occurring later in fetal development.

In some assessments, the population of interest is not available to monitor; in those situations, it would be useful for practitioners to understand when a different group could be used as a surrogate. For example, if it is not possible to monitor exposure in pregnant women, are women of reproductive age an appropriate surrogate? When making this determination, one must consider the numerous physiological changes that occur due to pregnancy and throughout pregnancy. It is of interest what surrogates EPA would consider appropriate.

**EPA Response:** Text not revised because this is beyond the scope of this document.

  

**Submitter:** U.S. Department of Defense (DoD)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** The stated principal focus is on non-occupational exposures, but occupational exposures should be addressed as well. There are EPA programs which include occupational exposures in their risk assessments, the TSCA Workplan Chemicals and the TSCA New Chemical Review Program, for example. Such exposures are relevant to include in these Guidelines to insure consistency in the Agency.

Please consider addressing occupational exposures, if there is existing guidance and procedures EPA endorses to address such exposures it should be cited. Please ensure, at the least, that a valid reason is given for excluding occupational scenarios, and the document acknowledges the reduced utility of the Guidelines without them.

**EPA Response:** Text not revised because the general principles regarding non-occupational exposures outlined in this document can be applied to occupational exposures.

**Submitter:** U.S. Department of Defense (DoD)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** While this document will provide an excellent resource for the experienced practitioner, its length and reliance on references (rather than providing the information in the text) hinder its utility for the average practitioner.

To better facilitate its use by the typical practitioner we suggest that a series of decision/flow charts at the beginning of the document (with hyperlinks to the main document) could provide both a guide and a general "checklist" for the practitioner who wants to determine if the major issues have been addressed.

**EPA Response:** Text not revised because this would extend the length of the document and a general overview model is provided in Figure 3-1.

  

**Submitter:** Utility Water Act Group (UWAG)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** The use of the Draft in the context of human health water quality criteria will have a direct impact on the members of UWAG and their obligations under the CWA. The Draft needs to be clearer on the relationship between the human exposure assessment concepts in the document and how those concepts are intended to be used in the implementation of the CWA's regulatory programs by EPA and the states. If EPA intends for the Draft to be used in the assessment of impacts on human health and risk management in a regulatory context, the final document should discuss human exposure assessment in the context of the specific statutory and regulatory requirements. Absent guidance from EPA, the final document has the potential to be misused, and there is a risk it could negatively impact the implementation of EPA and state environmental statutory and regulatory programs.

Further, EPA should acknowledge in the Draft that human exposure assessment and risk management decisions will be made by different regulatory agencies depending on the statutory structure of the specific program. For example, TSCA is a federal program that is implemented by EPA. However, the CWA employs a cooperative federalism structure where states have the authority to make human exposure assessments and decisions based on risk, subject to EPA oversight. The Draft should be explicit that human exposure assessments and any decisions based on risk in a statutory structure like the CWA may be made by the states, and that the Draft is not intended, nor should be interpreted, to in any way bind the states in their independent decision making based on unique state-specific considerations or otherwise limit their regulatory flexibility.

**EPA Response:** Text not revised because this document recommends coordination with the appropriate EPA program for specific guidance on the development of exposure assessments under legislative mandates.

**Submitter:** Utility Water Act Group (UWAG)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** The Draft and its discussion on human exposure is generic and non-context specific. This makes it difficult to determine exactly how the final document will and should be used by EPA, the states, and the public in the various environmental statutory and regulatory programs it may touch. For example, as worded, the Draft could be applied to any program that focuses on human exposure and protecting human health, including, but not limited to, the Clean Air Act, 42 U.S.C. § 109(b)(1) (“[n]ational primary ambient air quality standards ... requisite to protect public health.”), the Safe Drinking Water Act 42 U.S.C. § 300(g)-1(b)(4)(A) (“maximum contaminant level goal ... set at the level at which no known or anticipated adverse effects on health of persons occur...”), and the Toxic Substances Control Act (TSCA). 15 U.S.C. § 2603(a)(1)(A)(i) (“chemical substance ... may present an unreasonable risk of injury to health.”). For UWAG members, the primary concern is the CWA and how the Draft will impact the development, promulgation, and approval of human health water quality criteria as part of state water quality standards, and associated WQBELs in NPDES permits. There is no guidance in the Draft on how the final document should be used in the context of these environmental statutory and regulatory programs.

**EPA Response:** Text not revised because this document recommends coordination with the appropriate EPA program for specific guidance on the development of exposure assessments under legislative mandates.

**Submitter:** Virginia Department of Environmental Quality (DEQ)

**Topic:** Purpose and Scope

**Comment Type:** Public

**Comment:** While the guidance contains a large amount of good and useful information, it provides only limited direct guidance for parties interested in performing or reviewing the types of studies discussed. Discussions tend to be fairly generic and do not include specific recommendations. The document could be substantially improved by including more discussion of how the principles outlined in the document could be applied to common scenarios encountered by regulators and researchers.

**EPA Response:** Text not revised because this document recommends coordination with the appropriate EPA program for specific guidance on the development of exposure assessments under legislative mandates.

**Submitter:** Virginia Department of Environmental Quality (DEQ)

**Topic:** Purpose and Scope

**Comment Type:** Public

- Comment:** The target audience of this document is unclear. Is the document intended for facilities that would want to conduct such studies at a site, regulators reviewing these studies, university and/or research institutes that are developing these types of data, or all of the above? DEQ envisions the guidance being used frequently by regulators that are evaluating site-specific submissions to their programs, and who may not have a significant amount of experience performing or evaluating these types of studies.
- EPA Response:** Text not revised because the Executive Summary states that the intended users are all individuals conducting exposure assessments for or under the direction of EPA. Additionally, a recommendation is given to coordinate with the appropriate agency programs for specific regulatory requirements.