Summary Report of the Meeting to Peer Review the Draft Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water

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Notice

This report was prepared by Eastern Research Group, Inc. (ERG), a contractor to the U.S. Environmental Protection Agency (EPA), as a general record of discussion during the meeting to peer review the draft *Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water*. This report captures the main points and highlights of the meeting. It is not a complete record of all details discussed, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. Statements represent the individual views of meeting participants. Except as specifically noted, no statements in this report represent analyses by or positions of EPA or ERG.

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List of Acronyms

CARVER	Criticality, Accessibility, Recuperability, Vulnerability, Effect, and Recognizability
CFSAN	Center for Food Safety and Applied Nutrition
DALY	disability-adjusted life year
EPA	U.S. Environmental Protection Agency
ERG	Eastern Research Group, Inc.
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FSIS	Food Safety and Inspection Service
ILSI	International Life Science Institute
HIV	Human immunodeficiency virus
MRA	microbial risk assessment
NRC	National Research Council
ORD	Office of Research and Development (U.S. Environmental Protection Agency)
QALYs	quality-adjusted life year
SRA	Society for Risk Analysis
TCCR	transparency, clarity, consistency, and reasonableness
USDA	U.S. Department of Agriculture
WHO	World Health Organization

1. Introduction

The U.S. Environmental Protection Agency (EPA) and the U.S. Department of Agriculture (USDA) Food Safety Inspection Service (FSIS), along with scientists from other agencies, are leading an activity to develop a guideline for conducting microbial risk assessment (MRA). The draft guideline—*Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water*—is intended to improve transparency in how cooperating federal agencies conduct MRA and promote consistency in terms of approaches and methods, from the early planning stages for risk assessment projects through risk management and communication.

Eastern Research Group, Inc. (ERG), under contract to EPA, organized an independent peer review of the draft *Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water* (hereafter referred to as "the Guideline"). Nine nationally or internationally recognized experts (Appendix A) conducted this review:

- Darrell Donahue, Ph.D. (Chair)
- Louis Anthony (Tony) Cox, Jr., Ph.D.
- Joseph Eisenberg, Ph.D.
- Jeffrey Griffiths, MD, M.P.H.
- Mark LeChevallier, Ph.D.
- Patricia Meinhardt, MD, M.P.H.
- Christine Moe, Ph.D.
- Gary Sayler, Ph.D.
- Donald Schaffner, Ph.D.

This report documents the discussions and outcomes of the peer review, for which the peer reviewers both prepared written comments and participated in a one-day peer review meeting to discuss their findings.

1.1 Pre-meeting Process

ERG searched for and selected reviewers who had appropriate technical qualifications to conduct this review (based on expertise criteria provided by EPA) and who had no conflict of interest in performing the review. ERG provided the reviewers with the Guideline and a charge (Appendix B), which asked for their comments on various aspects of the document. All reviewers also received, for their consideration, copies of all written comments submitted during the public comment period (Appendix C).

In the first stage of the review, the experts worked individually to prepare written pre-meeting comments (Appendix D), which ERG then provided to all reviewers and EPA document authors prior to the meeting. ERG also facilitated a conference call with the reviewers and the EPA and USDA document authors to provide an opportunity for the authors to present background information on the review document and for reviewers to ask questions of clarification. Reviewers

then worked individually, without further contact with other reviewers or EPA, to prepare their pre-meeting comments.

1.2 Peer Review Meeting

In the second stage of the review, ERG convened a one-day peer review meeting on November 7, 2011, in Washington, DC. The meeting was attended by several observers (Appendix E), in addition to ERG staff. Appendix F provides the meeting agenda.

John Wilhelmi (ERG), the meeting facilitator, opened the meeting by welcoming the reviewers and observers, who included EPA and USDA document authors, other EPA staff, and interested members of the public. Mr. Wilhelmi asked the reviewers and EPA document authors to introduce themselves. Peer reviewers affirmed that they continued to have no conflict of interest in reviewing the Guideline. Mr. Wilhelmi noted that all meeting discussions would be conducted by the peer reviewers only. Reviewers could request, and observers could provide, clarifications where necessary and relevant; however, observers should not join the discussions. Mr. Wilhelmi then opened the meeting for oral public comment, but no observers commented. The attending document authors (Mike Broder, EPA/ORD; Kerry Dearfield, USDA/FSIS; and Nicholas Ashbolt, EPA/ORD) then made brief statements thanking the peer reviewers for their work.

Mr. Wilhelmi then turned the meeting over to Darrell Donahue, the designated chair, to begin the reviewer discussions, which covered the charge questions. At the end of the meeting, the reviewers developed a summary of their key findings, which are presented in Section 2 of this report. Section 3 presents a summary of the peer reviewers' discussions. After the meeting, reviewers were given the opportunity to revise or amend the written comments that they had submitted previously. However, none of the reviewers elected to do so.

2. Peer Reviewers' Summary

This section presents summary statements that the peer reviewers developed at the end of the peer review meeting. The following statements are organized by charge question and are presented exactly as they were displayed at the meeting, except for some minor editorial revisions. In the list that follows, "chapters" refer to the chapters in the Guideline.

Charge Question 1: Overall Format and Themes

- Use graphics throughout
- Cut and tighten text and overall comments
- Synthesize content presented in lists
- Add brief summaries at end of chapters
- Include bibliography with references for further information
- Review discussions on immunity throughout document to ensure text is accurate (refer to reviewers' written comments for specific examples)
- Review descriptions of immune status, how it is measured, and implications for MRA

Charge Question 2: Introduction (Chapter 1)

- Online tools should be mentioned (and how to access them)
- Uncertainty and variability:
    - Discuss how it impacts overall MRA
    - Move initial discussion to Introduction
    - Better distinguish the two terms
- Ensure that "why" and "when" for conducting MRAs is addressed
- Distinguish a pathway-based approach from an attribution-based approach (for further information, see the final bulleted point in the discussion summary for charge question 1D)
- Clarify the intended audience and write to that audience
- Define difference between population- and individual-level risk and dynamic versus static models
- Link to international picture in MRA activities

Charge Question 3: Planning and Scoping (Chapter 2)

- Improve organization of chapter by focusing on Section 2.6
- Implement good group dynamics, but avoid "groupthink"
- Include guidance for quick, quantitative risk assessments (or screening assessments)
- Delete the "CARVER plus Shock" text, but still note that vulnerability assessments may be conducted
- Discuss uncertainty about conceptual models (e.g., the correct conceptual model for a given MRA may not be known)
- Emphasize the iterative process

Charge Question 4: Hazard Identification and Hazard Characterization (Chapter 3)

- There is no correct answer about how best to split hazard identification and hazard characterization for MRAs. Options presented include:
    - Consider splitting sections on hazard identification and hazard characterization, and include dose-response as a sub-section in hazard characterization
    - It is neater to have a separate dose-response chapter
    - Consider organization used by ILSI
    - Consider strictly following the FAO/WHO format
- Expand discussion on environmental hazards in this section

Charge Question 5: Dose-Response Assessment (Chapter 4)

- Graphics and illustrations should support this discussion
- Include more discussion on uncertainty and variability in models
- Revisit use of one-hit, no threshold model as a recommended default
- Discuss R_0 and consider where secondary spread might fit in a reorganized chapter framework, possibly as a separate chapter altogether
- Consider attribution-based approaches

Charge Question 6: Exposure Assessment (Chapter 5)

- Transmission models need to be updated
    - Synthesize text across multiple chapters (exposure, dose-response, and risk characterization) on this topic
    - Another option is to move this entire topic to risk characterization
- Need to discuss fate and transport models
- Address data needs for environmental occurrence data
- Consider including an "Exposure Activities" section
- Include information on treatment processes

Charge Question 7: Risk Characterization (Chapter 6)

- Link risk characterization back to planning and scoping
- Secondary transmission needs to be addressed
- Include more examples of successful risk characterization

Charge Question 8: Risk Management (Chapter 7)

- Focus should be on the risk assessor
- Examples should be included
- Consider risk reductions and mitigations, rather than acceptable risk levels
    - "Bang for the buck": Where do you spend limited resources to most reduce risk?

Charge Question 9: Risk Communication (Chapter 8)

- This section should not be a primer on risk communication. It should focus on risk communication issues faced specifically by risk assessors, when working with risk managers.
- Include references (with links) to existing resources on risk communication.
- Place risk into context for stakeholders.
    - Distinguish risks to individuals (e.g., high-risk) from risks to populations (e.g., the "worried well")

Charge Question 10: Overarching Issues

- Exciting document as it shows harmonization among U.S. federal agencies
- Question-and-answer format allows for Guideline to be a living document

3. Summary of Reviewer Discussions

This section summarizes reviewer discussions at the peer review meeting, which provided the basis for reviewer findings presented in Section 2 of this report. The summary is organized by the charge questions, which are shown in ***bold italic*** font. At the meeting, the reviewers commented on each charge question, but not necessarily on every topic within each charge question. Several references are made to the peer reviewers' written comments, which are provided in Appendix D. This section documents the majority of comments made during the meeting, without attempting to assign priorities to individual suggestions or recommendations.

3.1 Charge Question 1: Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

- Multiple reviewers stated that, overall, the document format was useful and the question-and-answer format was easy to use. Several reviewers noted that the format resulted in some redundancies; one reviewer commented that such redundancies were not necessarily problematic, because they allowed sections to stand alone without forcing readers to reference text in other sections. Key benefits of the document's question-and-answer format cited by reviewers include:
  - Allowing for users to quickly identify a topic of interest, which is particularly valuable when time is a concern (e.g., in the middle of an outbreak investigation).
  - Supporting the concept of a "living" document, in which individual sections—or responses to questions—can be easily updated and revised as needed. New questions can also be added.
  - Serving as a readily transferable teaching tool.
- Multiple reviewers commented that most chapters were too long and could be significantly condensed without loss of important content.

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

- Multiple reviewers stated that the list of abbreviations should be moved to the front of the document.
- One reviewer noted that the organization of the glossary was good, and that the questions provided in the appendices were useful.

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

This topic was not directly addressed during the discussions at the meeting. Refer to the peer reviewers written comments (Appendix D) for responses to this question.

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

- Several reviewers emphasized the degree to which the document would benefit from the integration of examples into the text, noting that it would likely make the document appealing to a wider range of audiences. Examples and case studies could be inserted as text boxes, and should be selected to address various types of microorganisms and environmental media.
- The document varied greatly, one reviewer noted, in terms of clarity of writing and assumptions regarding the audience's technical aptitude. The reviewer encouraged that as much jargon as possible be removed. Where it was not possible to replace such terms, the reviewer stressed that the document must clearly define each concept, as a wide variety of people with varying backgrounds will read and use the document.
- A reviewer noted that many chapters have somewhat abrupt endings, without any synthesis of information presented earlier. This reviewer recommended that the authors add a short "conclusion" section at the end of each chapter in which key points would be concisely summarized or re-emphasized. The flow of each chapter would also be improved by placing a "for more information" section at the end of each chapter such that external references would not disrupt the flow of the text. In addition, multiple reviewers recommended that the references include hyperlinks to online resources.
- Multiple reviewers commented on the intended audience of the document and how the target audience affected the tone and structure of the document.
    - Several reviewers commented that the document should more explicitly define the intended audience. In particular, a reviewer noted that the intended audience is not entirely clear for the earlier chapters of the Guideline.
    - Several reviewers noted that while many different audiences will eventually access the document, the main audience should be considered risk assessors requiring more structured information on MRAs, and the entire document framed accordingly. The reviewers noted that the current organization of the document should generally be familiar to this audience.
- Several reviewers stated their appreciation that EPA and USDA collaborated and harmonized their approaches to MRA. One reviewer expressed a desire for the document to further its collaborative nature and have it better integrated with international guidelines, such as highlighting "Codex" and other prominent references.
- A reviewer cautioned the authors about being wary of the Guideline's file size, especially after graphics are added to the text. From experience, the reviewer noted, people are less apt to download a document if it has a prohibitively large file size.

- A reviewer noted that the Guideline is currently organized around a fairly conventional risk assessment approach, in which assessments consider how substances—in this case, microorganisms—move through the environment to receptors and the risks associated with those exposures. By following this approach, the Guideline fails to consider an important alternative: source tracking. The reviewer noted that not only is source tracking a viable approach, particularly for MRA, but it can also serve as an important alternative to the pathways approach when such pathways are difficult to decipher or data are unknown. Depending on the available data and the circumstances involved, this "backward" approach can be more useful than conventional "forward" approaches based on evaluations of different exposure pathways. The reviewer noted that the source tracking approach could be inserted as a standalone chapter, or that it could be integrated into chapters 1 or 2.
    - Another reviewer added that the entire field of epidemiology evaluates risks based on observed outcomes. The reviewer recommended broadening this recommendation of adding a chapter on source tracking to including more detailed discussion throughout the Guideline on the use of epidemiology in quantitative MRA; this reviewer noted that evaluations of outbreaks associated with recreational water exposures has very useful illustrative examples. Epidemiology can address some of the limitations of dose-response, especially in allowing for insight into risks for sensitive subpopulations.
    - Another reviewer suggested that this issue of different risk assessment approaches could be addressed by adding a chapter on "Non-traditional Risk Assessments," which could address attribution modeling, the role of epidemiology, and other modeling approaches. Another reviewer noted that some of the text in the current draft Guideline (see pages 106-107) could be used in this new chapter, if it is developed.

3.2 Charge Question 2: Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

- One reviewer stated that an introductory diagram illustrating the various components and processes of MRA would be highly valuable. An example cited is shown in the reviewer's written comments (see page D-82 of this report).
- A reviewer said the Introduction should include some information about how the Guideline fits into the international picture for MRA.
- Multiple reviewers recommended that the Introduction include a discussion of the online tools, databases, software and other resources available to risk assessors.
- A reviewer asked the document authors present at the meeting why the U.S. Food and Drug Administration (FDA) was not listed as a document author, especially considering that agency's experience with conducting MRAs. The reviewer recommended that the Introduction to the Guideline be revised to clarify what FDA's role was in developing the document.

- Several reviewers recommended briefly defining "uncertainty" and "variability" in the Introduction, and discussing how they relate to MRA. Reviewers noted that later sections of the document could then provide much more detailed information on uncertainty and variability in the context of dose-response, hazard characterization, and other topics. A reviewer suggested using a graphic to assist in the explanation. One reviewer noted that such a discussion should address the variability associated with assumptions regarding homogeneity when applied to heterogeneous populations and environments.
- A reviewer highlighted the fact that "risk assessment" and "microbial risk assessment" appeared to be used interchangeably throughout the document. Further, the reviewer noted that much of the section read as if it were a broader explanation of risk assessment as a whole; if such an approach were to remain, the reviewer emphasized that it should be made explicitly clear from the outset. Another reviewer stated that the document should work to specifically target MRA issues; therefore, passages clearly lifted from other efforts (e.g., sections pertaining to "conventional" risk assessment for carcinogens and noncarcinogens) should be deleted.
- Several reviewers discussed the TCCR criteria (transparency, clarity, consistency, reasonableness) presented in Section 1.10 of the Guideline. The reviewers discussed the extent to which "validation" should be addressed in this section, but differing opinions emerged:
    - One reviewer said that following the TCCR criteria, while desirable, does not ensure correctness of an MRA, which raised the question about where "validation" should be addressed in the Guideline. This reviewer added that some MRA predictions might appear to be reasonable, but the unpredictable nature of certain microorganisms can result in reasonable projections being incorrect. He recommended that the document authors include some text in the Guideline emphasizing the importance of validating MRA findings.
    - Another reviewer disagreed, noting that risk assessments rarely have the ability to perform validation because risks are so low. The reviewer referenced an article in *Science* from about a decade prior that discussed the difference between "validation," "verification," and "confirmation." He noted that many times risk assessors could only ensure a scientifically credible approach and look for consistency and reasonableness, though actual validation of predicted outcomes may not be possible.

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

- Multiple reviewers recommended that this chapter be thoroughly edited by a technical writer and significantly shortened. During the meeting, the peer reviewers identified several specific action items for the document authors:
    - Either delete or revise all sentences that include the word "appropriate" or "depend."
    - Search on all sentences that include the word "should," and clarify why a specific action should be done.

  - Revise Section 1.9 to better answer the question listed in the section title—currently the text lists the other guidelines, but does not adequately explain their relation to other frameworks.
  - Section 1.10 could be confusing to readers because it compiles many different lists of risk assessment principles, with no synthesis of information. A reviewer suggested distilling these lists into a few major points.
  - The peer reviewers referred to their written comments (Appendix D) for many additional examples of suggested editorial revisions.
- A reviewer recommended moving Sections 1.5 and 1.6 to the end of the chapter as they are currently poorly integrated into the text. The reviewer did note that if a conclusion section were added to each chapter—as had been previously recommended—then the sections may remain as they currently are.
- One reviewer questioned whether the term "life stage" is appropriate for humans, noting that the implied concept is more appropriately captured by the term "age class." The document authors were asked to clarify this issue, and an EPA observer indicated that the agency's Office of Children's Health routinely uses "life stage" when referring to certain sensitive subpopulations. Another reviewer added that documents published by the World Health Organization (WHO) also use this term in a similar fashion. Several reviewers eventually recommended that the authors should revisit this terminology, and consider including a footnote explaining subtleties in terminology should the Guideline continue to refer to life stages in humans. A reviewer further suggested that the document include a figure illustrating how susceptibility may vary not only with age but with other conditions (e.g., pregnancy, illness, frailty).

3.3 Charge Question 3: Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

- One reviewer said the Planning and Scoping chapter could be improved by including examples of how poor or incomplete problem formulation can compromise the relevance and value of MRAs. The reviewer explained, as an example, that interventions designed to reduce risks from one pathogen might inadvertently increase risks from other pathogens. The reviewer recommended that the guidance on Planning and Scoping should be revised to ensure that all significant and likely consequences of alternative risk management practices are considered, including unintended consequences of risk management decisions.
- A reviewer took exception with reference to "complete information" in the context of the value-of-information analysis (see Section 2.6.7 of the Guideline). He recommended that the document authors consider revising this entire section based on feedback provided in the reviewers' written comments (e.g., see pages D-7 to D-10 of this report).
- One reviewer noted that it is important to acknowledge that the correct conceptual model for some MRAs may not be known, due to limited or no information on exposure pathways and dose-response relationships. The reviewer therefore suggested that the Guideline should inform readers of the utility of using multiple plausible conceptual models, starting with the premise that more than one model could be considered for the risk assessment in

question and the preferred model may be uncertain at first. The reviewer also reiterated the importance of model validation, especially in circumstances where many conceptual models are being considered.

- One reviewer did not think Sections 2.3, 2.5, and 2.8 belonged in the chapter, because the topics addressed pertain to the overall risk assessment, and not the planning and scoping involved. The reviewer said these sections could be deleted or moved to other chapters, such as the Introduction.
- One reviewer highlighted pages 26 through 29 of the Guideline as being particularly useful. Similarly, another reviewer said Section 2.6 contains the most important content in the chapter.
- A reviewer noted that Section 2.3 should be considered through the lens of resource allocation as opposed to making a determination of whether or not a situation is "bad enough." Further, the section should revise its mention of the decision analytic framework "value of information," as the reviewer found the tool to be highly valuable (for more detailed commentary, see the written comments on pages D-7 to D-10 of this report). This reviewer also recommended that Section 2.2 include language cautioning risk assessors from falling victim to "groupthink."
- A reviewer noted that Sections 2.6.4 and 2.6.5 did not contain useful information, and should only remain in the document if their informative content is increased. In addition, the reviewer took issue with 2.6.5 measuring the "importance" of individual data gaps. Instead, the reviewer thought the topic should consider the significance of all data gaps taken together.
- The list of types of MRA in Section 2.5.2 does not include simple quantitative risk assessment. A reviewer recommended that this item be added to the list. During this discussion, the document authors clarified that this topic is covered under "screening risk assessments," which are mentioned in the text in question.
- Two reviewers recommended that discussions on "CARVER plus Shock" be removed from Section 2.5.3, or at least should be relegated to no more than a reference of "other available methods." Another reviewer found the concepts covered in Section 2.5.3 to be valuable, but more from the perspective of reducing risks associated with failures of water treatment and distribution systems as opposed to focusing on terrorist attacks. This reviewer encouraged the document authors to move this discussion to Chapter 7, as vulnerability considerations may be better addressed under risk management.
- A reviewer took exception to the statement that "expert judgment may offer the best available science…" (page 33 in draft Guideline). The reviewer noted that past experience suggests that expert judgment has not always been scientifically accurate in the field of MRA.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

- Consistent with the previous comment about the limited information on screening-level risk assessments, one reviewer said the document lacks detailed guidance for the individual who wants to perform an MRA in a short span of time. The reviewer noted that the chapter is

constructed under the assumption that multiple parties will undertake MRA and involve many workers; however, practical guidance is still needed on how to do a quick, useful, scientifically sound, but limited-depth MRA. Another reviewer echoed the concern, but wondered if such a request is out of scope in a federal workplace; regardless, the reviewer recommended that the Guideline either provide guidance on how to conduct quick, screening-level risk assessment or explain why that guidance is not being provided.

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

- Expanding on a comment raised earlier, a reviewer said the authors could improve the Planning and Scoping section by including examples of both successful and unsuccessful scoping efforts during risk assessments, highlighting the thorough considerations of the former and the inadequate preparations of the latter.
- A reviewer emphasized that conveying information about conceptual models is greatly enhanced through the use of pictorial representations. Such a figure, the reviewer explained, can serve as the common foundation from which multi-agency efforts are built.
- Multiple reviewers said the chapter would benefit from a significant technical edit, with changes to the overall structure and organization of material. Specifically, reviewers highlighted the following:
    - Chapter 2 includes multiple lists with steps in the planning, scoping, and problem formulation process (e.g., see Sections 2.1., 2.1.1, and 2.6). The reviewer recommended that the document authors develop a single list that incorporates problem formulation as one of the steps in the planning and scoping process.
    - Section 2.6 has the most useful information in the chapter and should be moved to the front such that the entire chapter is oriented around it.
    - The chapter should be restructured such that the "why" and "when" come first, followed by the "who," then followed by an explanation of "how" to conduct the planning and scoping.

3.4 Charge Question 4: Chapter 3 – Hazard Identification and Hazard Characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

- A reviewer stated that while it is appropriate to consider both the nature of a pathogen as well as the potential for adverse effects due to lack of treatment, the chapter does not pay enough attention to the latter. The reviewer noted that an increasing number of risk assessments are focusing on the potential cause of adverse effects (e.g., process breakdown, post-treatment contamination) and characterizing risks in the face of multiple unknowns. The reviewer added that this chapter could present more detailed information on how environmental factors impact microbial risk, drawing from examples in the published literature specific to hantavirus and Lyme disease.

- A reviewer noted certain concepts in the chapter that he did not think were relevant to hazard identification. Specifically, he said the topics covered under Sections 3.5 and 3.7 are not relevant to hazard identification in the context of MRA.
- One reviewer found the divisions between hazard identification and hazard characterization to be somewhat artificial. He added that the approach taken in the Guideline is a departure from what has been adopted by WHO/ FAO (Food and Agriculture Organization), in which dose-response is part of hazard characterization. The reviewer recommended that the authors clarify why different parties use different methods when distinguishing these risk assessment terms.
- One reviewer found the chapter to be important, but noted that it had the potential to be easily misunderstood by a reader. For example:
    - The reviewer found the differentiation between hazard identification and hazard characterization to be jargonistic and bureaucratic. He noted that the definitions used in the Guideline (see footnote on page 43 and text on pages 44-45) do not effectively distinguish these terms.
    - The reviewer found some definitions on pages 45-46 of the Guideline to be inaccurate or unclear; for example, using "random sampling" in the definition of genetic drift could confuse readers. This list of definitions should be revisited for technical accuracy.
- Two reviewers suggested several revisions to the chapter, largely to reduce the amount of unnecessary detail. For example:
    - Much of the text on page 48 of the Guideline, while perhaps interesting to a microbiologist, is likely too technical for the more general audience of risk assessors.
    - Table 3.1 should indicate which organisms are zoonotic, because this is a key factor involved in the risk assessment. The table should focus on microorganisms that are more common in the United States (e.g., consider adding *Shigella* and enteroviruses under their appropriate categories, and consider removing *Francisella tularensis* and *Brucella suis*). The table should also list examples of indeterminate agents, such as Brainerd diarrhea—a gastrointestinal syndrome believed to be caused by a microorganism, though the exact cause has yet to be identified. Other suggested revisions included: removing *Pfiesteria piscicid* from the table (reason not provided) and adding a new row for prions, due to evidence that variant Creutzfeldt-Jakob disease is caused by food-borne exposures.
    - The title for Section 3.7 should include the word "detect" to be consistent with the content of that section, and the title of Section 3.8 should be revised because "special concerns" is ambiguous.
    - Page 54 of the Guideline provides too much detail on typing methods. The text should provide general conceptual information on how typing methods can help inform a MRA, without going into the extensive technical detail.
- One reviewer said this chapter should encourage risk assessors to access and consider additional contextual information in the hazard characterization, such as influences of season, climate, and other external forces.

- A reviewer noted that the chapter emphasizes the importance of infectivity, but provides too limited information on environmental fate and transport. Points to add include discussing environmental conditions (e.g., temperature, acidity, moisture) that affect survivability of microorganisms. Though some of this information is found in Chapter 5, multiple reviewers noted that Chapter 3 may be a more important place for this context. More generally, one reviewer emphasized that full characterization of an organism is a key component element of the risk assessment, but Chapter 3 seems to focus largely on infectivity and pathogenicity, without considering other factors that ultimately contribute to risk. Another reviewer agreed that environmental fate and transport considerations are essential to risk assessment, but did allow that this chapter may not be the best location for covering the topic.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

- Several reviewers thought it was important for the chapter to only focus on hazard identification, instead of covering hazard identification and hazard characterization together. One reviewer viewed hazard characterization essentially as dose-response modeling. Further, the reviewer stated that the hazards should be identified based on the microbial agents themselves, not other factors that contribute to risk (e.g., a day spent in the hospital). While these other areas are key variables in a risk assessment, it is inappropriate to refer to them in hazard identification. Another reviewer concurred, stating that "hazard" is really defined as the source of a risk.
- On the other hand, another reviewer argued that the hazards identified by the current chapter format (including factors such as days spent in the hospital) are clearly important from a clinician's perspective, and thus supported the concept of including such factors (other than intrinsic properties of the organisms themselves) in the hazard identification and characterization steps.
- One reviewer suggested that the authors move much of the information that currently falls under "hazard characterization" into the hazard identification section.
- A topic raised several times was how to integrate population-level considerations (i.e., secondary transmission of disease) into the overall framework. The reviewers generally agreed that, for certain microorganisms, secondary spread must be characterized, understood, and modeled in a risk assessment—an issue that is unique when compared to chemical risk assessments. One peer reviewer said the Guideline as a whole could do a better job of explaining when and how secondary transmission should be considered in MRA, with special attention to quantitative aspects covered in the dose-response chapter. Further comment on this topic is summarized in the next section of this report.
- At the end of the meeting, the peer reviewers revisited the topic of how best to organize content into the categories of hazard identification, hazard characterization, and dose-response. The reviewers eventually noted that there is no single, correct approach for how to define these concepts in the context of MRAs. Some reviewers supported the approach currently presented in the Guideline (i.e., grouping together hazard identification and hazard characterization); others supported incorporating a revised organization (i.e.,

separating hazard identification and hazard characterization and moving dose-response into the new hazard characterization section); and other encouraged the authors to consider adopting the organization implemented by other parties (e.g., Codex, the International Life Sciences Institute [ILSI]). While these specific viewpoints differed, the reviewers generally agreed that the Guideline should be much more transparent in explaining why a certain framework was adopted and how that framework differs from those found in other major publications.

3.5 Charge Question 5: Chapter 4 – Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

- The reviewers revisited the issue of how secondary spread of disease in the population should be considered in the risk assessment framework. One reviewer noted that modeling disease spread in the population is clearly important and should be considered in the document, but he also argued that secondary spread of disease does not really fall under the concept of dose-response, at least as that concept has been articulated in chemical risk assessments. Another reviewer concurred, emphasizing that secondary spread of disease must be addressed in the Guideline; he acknowledged the difficulty of attempting to fit secondary spread of disease into a chemical risk assessment framework for which this concept does not apply.
- One reviewer noted that the chapter presents useful dose-response information for the initial route of infection, but does not adequately reflect the current state of the science for disease transmission modeling relevant to MRA. Written comments provided by the reviewers include several references for EPA to consider for updating the text on transmission modeling (see pages D-35 and D-36 of this report). Another reviewer supported the recommendation to provide more information on secondary spread, and added that some basic concepts can be used to highlight important points. For example, including some basic information on R_o—the basic reproduction number—and implications associated with R_o values being less than or greater than one would give at least some basic information on when secondary spread is important enough to include in MRAs. This reviewer also encouraged the document authors to consider incorporating concepts recently published by Peter Teunis regarding secondary spread during norovirus outbreaks.
- A reviewer recommended that the authors include examples in this chapter to illustrate when dose-response data have failed to successfully describe certain discrete events.
- Multiple reviewers noted that Chapter 5 would benefit greatly from use of more graphics. One reviewer encouraged graphical displays of different types of data distributions and dose-response functions. Another reviewer added that illustrations can be particularly effective when explaining how uncertainty and variability factor into risk assessment.
- Several reviewers took issue with the title of Section 4.1.2, which currently reads: "What is the one-hit model and why is it the preferred model?" One reviewer said a more appropriate title would be: "What is the one-hit model and *when* is it the preferred model?" The reviewer noted circumstances in which the one-hit model may not be the most relevant, such as for microorganisms that trigger host responses. The reviewer also noted that other

types of models may be more appropriate for certain bacteria of great interest, including *Campylobacter*. In short, the reviewer recommended that the authors better justify why they think the one-hit model is the preferred model, and under what circumstances. Another reviewer concurred, noting that this particular section was quite prescriptive, which was not consistent with other sections of the Guideline. All reviewers discussing the issue stated that additional explanatory text should be included if the authors continue to label the one-hit model as the preferred dose-response model. [Note: When reviewing a draft of this summary report, a peer reviewer indicated that the topic of preferred dose-response models was raised during the Society for Risk Analysis (SRA) 2011 Annual Meeting, which took place after the peer review meeting. Some discussion at that SRA meeting supported use of threshold models for MRA, which further underscores the need for the document authors to revisit the assumption of a one-hit, no threshold model. However, no specific citations were provided.]

- Revisiting a topic raised earlier in the meeting, two reviewers noted that the dose-response chapter may be an appropriate place to discuss the role of attribution-based models in MRA. One reviewer said these models may be useful for scenarios with extensive outbreak data but limited dose-response information, but risk assessors should be encouraged to evaluate the theoretical basis for these models (as with any model) before applying them to risk assessments.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

- A peer reviewer identified the following dose-response models that should be added to Table 4.1 in the Guideline:
    - *E. coli* O157:H7 models developed by Cassin et al. (see International Journal of Food Microbiology, 41:21-44) and Powell et al. (see Quantitative Microbiology, 2(2):141-163)
    - *Salmonella* model developed by FAO/WHO (no reference provided)
    - Multiple models for *Listeria monocytogenes* (no reference provided)
- One reviewer noted that the dose-response models included in the chapter largely focused on ingestion, which is appropriate given the Guideline's focus on food and water. However, he recommended that the chapter acknowledge that inhalation and dermal routes can also be important for MRA.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

- Given that no research will ever be conducted on the effect of *Listeria monocytogenes* on the human fetus, a peer reviewer recommended that EPA consider findings published by Dr. Mary Alice Smith on *Listeria monocytogenes* in monkeys. One reference provided was: Infection and Immunity, 76(2):726-731. Other reviewers agreed and encouraged the

document authors to consider animal studies in instances where human information are not available, but also cautioned against applying microorganism dose-response data from animals to humans, given the inter-species differences in infectivity and other parameters.

- Other reviewers supported the use of animal data and *in vitro* data in MRA, but only for limited insights (e.g., understanding how virulence varies across different strains of a microorganism). These reviewers generally did not support extrapolating dose-response data from animal studies to humans, as is routinely done for chemical risk assessment. However, one reviewer noted that animal dose-response models might have greater utility for certain combinations of species and microorganisms (see page D-53 in the reviewers' written comments in Appendix D). Should animal data be used in MRA, the reviewers emphasized the importance of acknowledging the uncertainties and limitations.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

- The reviewers expressed different opinions on the extent to which the Guideline should address uncertainty and variability. One reviewer said it was most important for the Guideline to clearly define the terms and describe any special nuances for how uncertainty and variability uniquely affect quantitative MRA. The Guideline need not be a definitive reference on uncertainty and variability, and should direct readers to other references for further information on the topic. Another reviewer agreed, and listed some examples of simple displays that can help illustrate basic concepts about uncertainty and variability (e.g., dose-response curves with and without variability and uncertainty).
- A reviewer recommended that the Guideline acknowledge some additional sources of uncertainty, such as those associated with low-dose extrapolation, host susceptibility, classification of subjects as being "infected," and dose measurements due to tittering of the inoculums used in the studies.
- One reviewer noted that the concepts of uncertainty and variability apply to many topics throughout the Guideline, and not just to dose-response models. This reviewer said that if these concepts were well defined and clearly articulated in the Introduction of the Guideline (as proposed earlier in the peer review meeting), then uncertainty and variability could be more easily addressed in the later report sections.
- A reviewer found some of the text on uncertainty and variability in Chapter 4 to be too technical for readers who are not statisticians. He identified Sections 4.2.1 and 4.2.4 as being particularly technical and candidates for a rewrite, especially if the target audience for the Guideline is risk assessors. This reviewer also found some statements in Section 4.2 to be confusing and inconsistent (see page D-36 of the reviewers' written comments in Appendix D).

3.6 Charge Question 6: Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

- One reviewer noted that the Exposure Assessment chapter does not present any information on environmental fate and transport models, which can be critical for MRA. He recommended that information on environmental fate and transport be presented in Sections 5.2.2 and 5.2.4.
- A reviewer commended the authors for including information on transmission modeling in Section 5.2.7, but he found the text and references in that section to be out-of-date. The reviewers' written comments (see pages D-37 and D-38 of this report) list several recent references that address transmission modeling, including consideration of the role the environment plays in secondary spread. Section 5.2.7 should be revised to acknowledge these models. Another reviewer agreed with these points, and further recommended that the authors revise this section to better address qualitatively how various factors affect disease transmission, such as immunity (and how immunity can vary with time for certain pathogens) and the importance of new persons entering a population. This reviewer said the Guideline could benefit from having an appendix that addresses some of these concepts, possibly by presenting a primer on infectious diseases epidemiology.
- One reviewer noted that the chapter made poor use of the word "may," rendering otherwise clear sentences ambiguous. The reviewer advised the document authors to search on this word throughout the chapter and revise text as necessary.
- The document provides an opportunity to give guidance not just to risk assessors, but also to those generating data (e.g., those conducting environmental sampling studies). A reviewer said it would be highly useful for those collecting data to know the degree of environmental sampling data required to support a quantitative MRA.
- A reviewer said the chapter does not adequately address the concept of "recurring exposures." To the contrary, the Guideline includes statements that seem to downplay the role that recurring exposures may play (e.g., "MRA is typically only concerned with single event exposures," page 87). The reviewer listed examples where repeated exposures and recurring events can be important for MRA (e.g., a water supply that is contaminated for several days, fomites that carry infectious agents for days).
- A reviewer stated that the chapter is far too long. He recommended a much shorter presentation on important exposure assessment principles that are most relevant to MRA. The chapter could end with a list of exposure assessment references that readers can access for more detailed information.
- One reviewer said Chapter 5 included some terminology that does not capture specific technical issues for food MRAs. Specifically, he said the chapter should include some discussion on prevalence of microorganisms, and he found the text on "sources" and "source evaluation" to have limited relevance to food MRAs.
- The reviewers briefly discussed concepts raised in the following written public comment submitted by Health Canada: "Section 5.4: Would it be possible to assign a qualitative description (low, medium, high) to the overall likelihood of exposure at the end of a microbial risk assessment? If yes, how? Would this be useful in risk communications to the public?" One reviewer found the concept of assigning qualitative exposure categories appealing, particularly in the context of risk communication to the public. However, another reviewer cautioned that attempts to translate data into generic qualitative categories tend to oversimplify results, sometimes at the expense of valuable quantitative insights. These two reviewers noted that the concept of using qualitative descriptors for exposure

and risk might be better suited for the chapter on Risk Communication. Further comments on this topic are summarized later in this report.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

- One reviewer recommended that a paragraph be added to the Guideline on use of regional sensitivity analysis to examine uncertainty in exposure assessment. He said this approach is particularly useful in cases where only qualitative, limited data are available.
- Chapter 5 largely focuses on exposure routes and pathways. A reviewer said this focus is appropriate, but encouraged the document authors to consider adding text about exposure activities that may be relevant to MRAs. Examples of such activities included using manure to fertilize a garden, cleaning a cat litter box, visiting a petting zoo, and living with a child who attends daycare. Another reviewer supported this recommendation, noting that these activities are important from a clinical perspective. Some discussion followed about the extent to which some of these activities (e.g., visiting a petting zoo) fall under the purview of federal regulatory agencies, but reviewers noted that the source of contamination in certain cases (e.g., water used to clean animals) clearly falls under EPA's mandate, even if the agency may not routinely evaluate health risks associated with exposure activities like visiting petting zoos. The two reviewers continued to support the recommendation to include information about exposure activities, but they also said that this content could also be placed in Chapter 6 (Risk Characterization).

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

- One reviewer recommended that Chapter 5 be expanded to include several additional topics, including characterization of model uncertainty, heterogeneity of exposures, and robustness of exposure estimates. This reviewer provided several other suggestions about how the Guideline can better cover the topics of uncertainty and variability in the context of exposure assessment. Those suggestions appear in the reviewer's written comments (see page D-12 of this report).

3.7 Charge Question 7: Chapter 6 – Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

- Section 6.5 in the Guideline suggests that risk characterizations can be "qualitative" or "semi-quantitative." The distinction between these terms was not clear to a reviewer, who

recommended that the authors clearly define what the two terms mean and how they differ. Further, the reviewer recommended that the authors revise the first sentence in the second paragraph in Section 6.4, because that sentence can be inferred as suggesting that risk is not a probabilistic concept.

- A reviewer said Chapter 6 in the Guideline was far better formulated than the previous two chapters, and the chapter should not require as extensive technical editing. Further, the chapter serves as a good model for the rest of the document in terms of effectively integrating examples into the text. Another reviewer said the figures in this chapter (especially Figure 6.2) were very useful.
- Several reviewers discussed the document's presentation of information regarding quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs). One reviewer suspected that some readers might have difficulty following the discussion of QALYs and DALYs in Chapter 7, because these terms had not been introduced and defined earlier in the Guideline. The reviewer recommended that the document authors either move this particular discussion to an appendix or, if the discussion is to remain in Chapter 7, provide additional background information on these terms earlier in the Guideline. Another reviewer concurred, adding that Chapter 7 should explain when it is appropriate to use these particular outcomes, what their associated strengths and weaknesses are, and how they are typically derived, because these concepts are not explained elsewhere in the document.
- A reviewer said equation 6.1 in the Guideline is incorrect. He referred to his written comments (see page D-13 of this report) for further clarification.
- When answering this charge question, reviewers revisited the idea of using qualitative categories for risk characterization (i.e., breaking risks into "high", "medium", and "low" categories). While acknowledging that breaking risks into simple categories may be useful for communicating to the public, one peer reviewer again voiced concern that attempts to map complex quantitative results into a few loosely-defined categories can lose valuable insights that are critical to effective risk characterization. Another reviewer agreed, but noted that the approach of discretizing risks may be useful to include in the Guideline, provided the Guideline cautions about pitfalls associated with this technique (e.g., the detail lost when attempting to use few categories to characterize complex risk distributions).
- The reviewers also revisited an earlier discussion about the extent to which the Guideline addresses secondary transmission, particularly with respect to Sections 6.5.1 and 6.5.2. One reviewer identified a few sentences in Section 6.5.1 as being inaccurate or not carefully worded, such as: "A static model would be appropriate in those cases where the central question is concerned with the probability of infection or illness relative to the dose of pathogens acquired from a single exposure." And: "Static models are useful for analyzing situations where the effect of an intervention directed to individuals is more important than the effect on transmission throughout the population." The reviewer gave examples where these statements were not accurate (see the reviewers' written comments on pages D-39 and D-40 of this report).
- A reviewer identified some technical issues associated with Figure 6.2 in the Guideline. For instance, the diagram currently conveys that the "post-infection" group is immune from future infection; however, depending on the microorganism and other factors, protective immunity may not develop after an infection and an individual may become re-infected in the future. The reviewer recommended that the authors revise the figure or annotate it to

acknowledge this issue. The text throughout this section should be reviewed by a microbiologist to ensure that it is technically correct when describing concepts like immunity, protective immunity, and immune status. For example, the presence of serum antibodies to a particular microorganism does not necessarily mean that a person is immune to future infections. It simply means that they were infected with that organism and developed antibodies against that organism. Another reviewer agreed, but again noted that some of these concepts could be addressed by developing a new appendix in the Guideline that addresses some fundamental concepts of infectious diseases epidemiology.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

- The document authors present at the meeting asked the peer reviewers for examples of published documents that the Guideline could cite as "gold standards" for quantitative MRA. The reviewers provided three responses:
    - FDA's risk assessment on *Vibrio parahaemolyticus* in raw oysters
    - Two reviewers suggested that the Guideline include a case study or other illustrative information for *Cryptosporidium*. This organism is currently not covered extensively in the Guideline, but dose-response curves have been published for different *Cryptosporidium* species and also for different isolates within the same species. Reviewers suggested that the authors consider incorporating some type of example in the Guideline about assessing risks from Cryptosporidium in water supplies.
    - One reviewer also recommended that the document authors consider presenting information on a FAO's *Salmonella* risk assessment, because that was a case where the Beta Poisson dose-response model was found to provide a very poor fit to observational data.
- Another reviewer recommended that the authors consider incorporating an example in the Guideline that illustrates secondary spread of disease accounting for the majority of population risk for a microorganism. Such an example would be particularly useful in highlighting how MRA can differ from conventional chemical risk assessments. This reviewer again noted that such a case study could be included in an appendix presenting general information on infectious disease epidemiology.
- At this point, a reviewer summarized a series of comments that were being made when responding to multiple charge questions. He noted that the Guideline eventually must convey to the reader the important differences between individual-level risk and population-level risk and the differences between a static assessment and a dynamic assessment. He said the draft Guideline already addresses these topics to a certain extent, but needs to do a much better job of this across all of the chapters. Some reviewers recommended that these issues could be addressed in a new appendix that offers a primer on infectious disease epidemiology, while others said the authors should consider weaving the concepts directly into the chapters throughout the Guideline.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

- Several reviewers noted that risk characterization ultimately should link back to problem formulation statements originally articulated in the MRA planning and scoping phase. They recommended that the Guideline emphasize this point, indicating that risk assessment should be an iterative process.
- Section 6.8 of the Guideline is titled: "How can a risk assessment be validated?" One reviewer commented that this section and other parts of the Guideline conflate the terms "review" and "validation." He emphasized that review is definitely not a substitute for validation, and this concept needs to be clarified in the document. Commenting on the same section, another reviewer said a more appropriate title would have been: "Can a risk assessment be validated?" This phrasing would help inform readers that it may not be possible to validate some MRAs.
- Section 6.6 of the Guideline addresses how sensitivity analyses and uncertainty analyses can factor into risk characterization, and the section included a table that identifies four approaches commonly used to conduct these analyses. A reviewer found it appropriate to addresses these types of analyses in risk characterization. However, this reviewer said that the table should not only list the different quantitative approaches but should also provide further context on these approaches (e.g., when and why are they appropriate for a given MRA).

3.8 Charge Question 8: Chapter 7 – Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

- A reviewer commented that Chapter 7 in the Guideline is generally well written, captures most major points, and seems to have been written by someone familiar with the risk assessment process. One concept that could be more prominently acknowledged is the fact that risk managers make decisions in the face of uncertainty, and one of the purposes of the risk assessment is to identify and characterize the underlying uncertainties.
- Several reviewers recommended that this chapter include examples or case studies to illustrate effective risk management decisions based on MRA, such as:
    - A peer reviewer recommended including the example of managing *Campylobacter* in chickens in Denmark. The reviewer explained that the government implemented a program that requires regular sampling of flocks. When a flock has a positive test result, its chickens must be sold frozen; and when samples are negative, the chickens can be sold fresh (and typically at a higher price).
    - Another example mentioned was management of *Salmonella* in the United Kingdom, where chickens are immunized against *Salmonella*, which results in marginally increased costs but greatly decreased rates of chicken-borne *Salmonella*.

- Chapter 7 includes several long lists, without any synthesis of key points at the end of the lists. Consistent with comments raised earlier in the meeting, a reviewer recommended that the document authors include some synthesis of information following lists in this chapter.
- Some text in Chapter 7 refers to establishing "acceptable" or "tolerable" levels of risk. One reviewer cautioned against this language for reasons listed in his written comments (see page D-13 of this report). Ultimately, the reviewer advocated for having Chapter 7 present a "decision-analytic approach" to risk management, which would focus on identifying the optimal decision from a range of options, rather than trying to identify an "acceptable" level of risk.
- Some reviewers had questions about the intended target audience of Chapter 7. Their impression was that this chapter was written for both risk assessors and risk managers, which conflicted with their impression of the target audience for the entire Guideline (risk assessors). The reviewers said the content in the Chapter was appropriate and there was no need to remove content, but the Chapter should be better organized such that language and guidance directed at risk managers is clearly separated from that intended for risk assessors.
- A reviewer noted that numerous external resources are available for topics covered elsewhere in the Guideline (e.g., dose-response, exposure assessment). However, far fewer resources are available to help risk assessors communicate with risk managers, particularly in the field of MRA. Accordingly, it is particularly important for Chapter 7 to provide effective guidance to microbial risk assessors.
- The first paragraph in Section 7.2 (page 150 of the Guideline) describes how risk managers can be involved in MRAs. One reviewer recommended that this text refer back to the initial MRA planning and scoping phases (Chapter 2 of the Guideline) to emphasize that risk managers should be involved throughout the process, and not only at the end—which may be implied by placement of the risk management chapter at the end of the Guideline. This reviewer also recommended that this section refer readers interested in additional information to the National Research Council's 2009 report on *Science and Decisions: Advancing Risk Assessment*.

3.9 Charge Question 9: Chapter 8 – Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

- The reviewers initially discussed the extent to which risk assessors would be expected to be responsible for risk communication. Some reviewers noted that many federal agencies have outreach and communication specialists and public affairs officials who are responsible for communicating directly with the public and the media—in which case, some of the content in Chapter 8 would not be applicable. However, Chapter 8 did not clearly articulate these anticipated roles and responsibilities. The reviewers recommended that the chapter first describe the types of risk communication that risk assessors are expected to conduct, and the document authors could then tailor the remaining content of the chapter accordingly. For example, the peer reviewers noted some content in Chapter 8 that should be deleted

(e.g., the text pertaining to communicating risk to young children) or revised (e.g., the text in list item (b) in Section 8.1 could be revised to explain that informing the public about risk may not be the risk assessor's responsibility).

- The reviewers had differing opinions on the extent to which the Guideline should offer guidance on risk communication. One reviewer found the chapter appropriate and commended the authors for developing a useful primer for risk communication. On the other hand, another reviewer was not convinced that a primer on risk communication was appropriate for the Guideline; he recommended that the chapter instead direct readers to published references on risk communication for further insight on the topic, rather than attempting to address the issue in great detail.
- One reviewer noted that risk communication needs and challenges will vary from one audience to the next. For instance, risk communication to the "worried well" is typically very different from risk communication to susceptible groups. The reviewer recommended that this concept be addressed in Chapter 8, with the main point being that risk communication should place risks into context (e.g., placing risks that one faces in context with other risks present in life). Another reviewer added that the chapter would benefit from presenting information on specific risk communication techniques (e.g., use of risk ladders).
- The document authors asked the reviewers for specific examples of effective risk communication for MRA. Some reviewers said the list included on page 161 in the Guideline contained useful information on the contents of risk communication. They also provided two specific examples of other documents to cite:
    - One example provided was FDA's *Listeria monocytogenes* risk assessment, where risk assessors communicated a risk ranking and its associated uncertainty bounds, which risk managers reportedly found to be exceptionally helpful.
    - Another example is FDA's *Vibrio parahaemolyticus* risk assessment, which communicated how risks would vary depending on chilling times, refrigeration temperatures, and other factors. Such information allowed users of the risk assessment to decide what actions to take to reduce risk.
- One reviewer said the chapter generally worked well for him, and that the content was consistent with his expectations. The one topic this reviewer said should be covered further in Chapter 8 is risk communications pertaining to cost-benefit analysis (e.g., effectively communicating situations where risk reduction strategies are not implemented due to the costs involved).

3.10 Charge Question 10: Overarching Issues

10A. Overall utility of the Guideline

- One issue the reviewers discussed was the need for more examples throughout the Guideline. While the reviewers generally agreed that the document should include more "good risk assessment" examples throughout, they had differing opinions on whether the document should also include "bad risk assessment" examples. One reviewer agreed that discussing "bad risk assessment" examples can have instructional value, but he was

concerned about the Guideline (and the associated federal agencies) placing such labels on prior risk assessments.

- A reviewer expressed concern that the document referenced the recent expert elicitation on fine particulate matter ($PM_{2.5}$) as a model example of how expert judgment can be used to inform the risk assessment process; however, the reviewer found that to be an example of precisely what can go wrong with expert elicitation. The reviewer recommended that the Guideline present the benefits and potential detriments associated with expert elicitation, without necessarily endorsing its use.

10B. The flow and continuity of the document

- A reviewer repeated a comment from earlier about ensuring that the many lists used throughout the document are followed with text that synthesizes the information. The reviewer added that synthesis statements (or paragraphs) should be included at the end of the Chapters throughout the Guideline. Another reviewer agreed that the Guideline presented numerous lists, with limited synthesis. This reviewer said many of these lists can be shortened, combined, or removed without loss of content.
- A reviewer noted a lack of integration between chapters. For example, the topic of uncertainty and variability is mentioned in nearly every chapter, but no reference is made in the different chapters of it having been previously discussed; also, the level of technical detail on these topics varies considerably from one chapter to the next. For topics covered throughout the Guideline (e.g., uncertainty and variability), the reviewers recommended that the issues first be introduced and defined in the Introduction; the authors should then ensure the text throughout the other chapters presents complementary material.

10C. The consistency of the document, both in language and level of detail, across the chapters

- A reviewer commended the authors for developing a Guideline that reflects "best practices" in risk assessment, risk management, and risk communication. The reviewer noted that the Guideline reached an appropriate balance between summarizing technical information while providing enough level of detail for the risk assessor audience.
- Another reviewer offered suggestions for the authors to consider when developing the next draft of the Guideline. These included avoiding passive language, incorporating synthesis statements throughout, and avoiding a simple rehashing of references.
- A reviewer recommended that the Guideline, after its content is finalized, undergo graphic design or desktop publishing to enhance its visual appeal, by incorporating diagrams, figures, text boxes, and more. Another reviewer agreed, adding that a more visually appealing document could make the Guideline more accessible to a broader range of stakeholders.

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors)

- It was difficult to comment on whether the document applies to stakeholders, when the Guideline is not explicitly clear on what is meant by “stakeholders.”
- A reviewer said that the document, or a subset of it, would likely be a valuable resource not only to risk assessors, but also to many additional stakeholders (e.g., non-governmental organizations, legislative technical committees).

Appendix A: Peer Reviewers

Peer Review Meeting for EPA's Draft Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water

L'Enfant Plaza Hotel
Washington, DC
November 7, 2011

Peer Reviewers

Louis Anthony (Tony) Cox, Jr., Ph.D.
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Denver, CO

Darrell W. Donahue, Ph.D., CQE *(Panel Chair)*
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Christine L. Moe, Ph.D.
Eugene J. Gangarosa Professor of
Safe Water and Sanitation
Director, Center for Global Safe Water
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Beaman Distinguished Professor of Microbiology
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Professor and Extension Specialist in Food Science
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Appendix B: Charge to Peer Reviewers

Technical Charge to External Peer Reviewers

Contract No. EP-C-07-024
Task Order No. 124
October 3, 2011

External Peer Review of EPA's Draft Microbial Risk Assessment Guideline: Pathogenic Microorganisms with a Focus on Food and Water

BACKGROUND

Over the past several years, scientists from the U.S. Environmental Protection Agency and the U.S. Department of Agriculture Food Safety Inspection Service along with scientists from other agencies, have been involved in the development of a draft Microbial Risk Assessment (MRA) Guideline. The MRA Guideline is intended to be a resource for U.S. Federal Government risk assessors, and their agents, contractors, and the general risk assessment community. In recognition of the needs and mandates of different Agencies and the various statutory authorities that may apply to microbial risk assessment, the Guideline emphasizes the need for a flexible template for conducting microbial risk assessment. Therefore, it is expected by the authors of this Guideline that fundamental concepts addressed here are intended to be applicable across multiple and diverse Federal missions. This Guideline is broadly focused on infectious diseases associated with the gastrointestinal tract and fecal/oral transmission in mainly food and water.

The Guideline is intended to be a living document and as more information becomes available, it can be modified and appropriate modules for this guidance can be added and revised. Therefore, this document provides a framework on to how to plan, assess, and analyze the potential for infection or diseases from exposure to microorganisms.

After this external peer review, the interagency workgroup will make essential modifications to the Guideline and will then provide an opportunity for all the interested Federal agencies to endorse the Guideline for their use. The final version will be made publicly available on the U.S. Environmental Protection Agency and U.S. Department of Agriculture web sites as well as any other Federal agency that endorses the Guideline for their use.

GENERAL INSTRUCTIONS

Please provide detailed explanations for responses to the charge questions, and focus any recommendations on improving the use, technical robustness, clarity, and efficacy of the MRA Guideline as a resource for guidance or support in conducting microbial risk assessments. Please organize your comments in the same order as the charge questions as all comments will be compiled into a pre-meeting comment booklet to be distributed to all panel members and EPA prior to the public meeting.

For specific comments, reviewers should clearly identify the point of reference in the document by referencing the report section and specific line and page numbers as part of your response.

If a question is outside your area of expertise, please indicate that by inserting these words "No response as this is outside my area of expertise."

CHARGE QUESTIONS:

The following non-prioritized list of issues for review has been prepared to help the interagency workgroup improve the MRA Guideline's effectiveness for users. The focus of the Guideline is to support professional microbiologists and risk assessors conducting risk assessments of pathogenic microorganisms in food and water.

1. **Overall Format**

   The major focus of the Guideline is in chapters 2, 3, 4, and 5. Chapters 6, 7, and 8 are provided to assist risk assessors about how to characterize and transmit the findings of the risk assessment.

   1A. Please review and comment on the usefulness of this format and ease of use.

   1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

   The intent of this Guideline is to provide guidance on microbial risk assessment with an emphasis on pathogenic microorganisms in food and water. However, it is expected that this document will have application to other scenarios, circumstances and regulatory context.

   1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

   1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

2. **Chapter 1 – Introduction**

   Chapter 1 essentially outlines the need for this Guideline. A concise background is also provided.

   2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

   2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

3. Chapter 2 – Planning and Scoping

It is clear from the recent National Research Council report *Science and Decisions* and other recent publications that planning and scoping before embarking on a risk assessment effort is a critical part of the entire process. This chapter outlines the critical processes that should be considered in setting up and conducting a MRA.

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

4. Chapter 3 – Hazard Identification and Hazard Characterization

Risk assessment approaches for microbes often begin with hazard identification. This chapter attempts to frame hazard in two ways, as the nature of the pathogen itself and also its potential to cause an adverse effect.

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

Past risk assessment paradigms for MRA usually tie hazard characterization with dose-response. However, the workgroup felt that combining hazard identification and hazard characterization together made for an improved description of the hazard. Dose-response and its associated modeling approaches are best presented in a separate chapter.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

5. Chapter 4 – Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

6. Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

7. Chapter 6 – Risk Characterization

Risk characterization guidance has been provided in greater detail elsewhere (e.g., EPA's Risk Characterization Handbook). This chapter is presented as a distillation of that guidance to give a microbial risk assessor an understanding about how to apply the analyses from Chapters 3 - 5 to prepare an appropriate risk characterization and to address the questions posed during planning and scoping. It is proposed that if greater detail is needed by a risk assessor, they could go to the referenced risk characterization guidance provided.

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

8. Chapter 7 – Risk Management

This chapter provides information to risk assessors about why they are conducting a risk assessment and what they need to be aware of when interfacing with risk managers and decision makers. It is not intended to be a fully detailed guidance on risk management itself.

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

9. Chapter 8 – Risk Communication

This chapter provides information to risk assessors about how and where the risk assessment they generated could be communicated to the various stakeholders interested in the risk assessment. It is intended to give basic information on risk communication responsibilities for the risk assessor, and not be guidance on risk communication itself.

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

10. Overarching Issues

The workgroup would like feedback on the quality of the draft Guideline. Please identify and provide the rationale for any suggestions on the following:

10A. Overall utility of the Guideline,
10B. The flow and continuity of the document,
10C. The consistency of the document, both in language and level of detail, across the chapters,
10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors).

Appendix C: Written Public Comments

PUBLIC COMMENTS SUBMITTED TO EPA FOR

MICROBIAL RISK ASSESSMENT GUIDELINE:

PATHOGENIC MICROORGANISMS WITH

FOCUS IN FOOD AND WATER

Docket ID: EPA-HQ-ORD-2011-0532

July 26, 2011 to September 26, 2011

usacitizen1 usacitizen1
<usacitizen1@live.com>
07/26/2011 05:28 PM

To Docket ORD@EPA, Michael Broder/DC/USEPA/US@EPA, <americanvoices@mail.house.gov>, <comments@whitehouse.gov>

cc

bcc

Subject PUBLIC COMMENT ON FEDERAL REGISTER FW: usda works solely for food profiteers, not at all for consumer safety or health

THIS BRINGS UP THE QUESTION OF HOW WE KEEP THOSE ALLEGED "BIOSECURE" HENS AND EGGS WHERE VACCINES ARE GROWN FREE FROM THESE MICROBES. NOBODY HAS EXPLAINED THAT TO ME AS YET, ALTHOUGH I HAVE BEEN ASKING QUESTIONS FOR TWO YEARS NOW.

I AGREE THAT WE NEED TO HAVE DATA ON MICROBES AND THEIR EFFECTS ON PRODUCTS, THINGS, PEOPLE, BUT SINCE VACCINES ARE BEING MANDATED FOR OUR CHILDREN, WILL YOU PLESE SEND ME INFORMATION ON HOW WE KEEP MICROBES OUT OF THE ALLEGEDLY "BIOSECURE" HENS AND EGGS AT THESE "BIOSECURE FACILITIES IN CHINA? OR ARE THEY IN THE USA?

JEAN PUBLIC ADDRESS IF RQUIRED

Date: Tue, 26 Jul 2011 06:50:38 -0700
From: jeanpublic@yahoo.com
Subject: usda works solely for food profiteers, not at all for consumer safety or health
To: usacitizen1@live.com

[Federal Register Volume 76, Number 143 (Tuesday, July 26, 2011)]
[Notices]
[Pages 44586-44587]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2011-18879]

ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-ORD-2011-0532; FRL-9443-9]

Notice of Availability of the External Review Draft of the Microbial Risk Assessment Guideline: Pathogenic Microorganisms With Focus on Food and in Water

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of document availability for public comment.

SUMMARY: The U.S. Environmental Protection Agency (EPA) is announcing a 60-day public comment period for the External Review Draft of ``Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and in Water.'' EPA developed the Guideline in collaboration with the U.S. Department of Agriculture, Food Safety Inspection Service (USDA/FSIS) and with scientists from other Federal agencies. This draft document is being released solely for the purpose of seeking public comment prior to peer review. The document will undergo independent peer review during an expert peer review meeting,which will be convened, organized, and conducted by an EPA contractor in 2011. The date of the external peer review meeting will be announced in a subsequent Federal Register notice. All comments received by the docket closing date September 26, 2011 will be shared with the external peer review panel for their consideration. Comments received after the close of the comment period may be considered by the two agencies when they finalize the document. This document has not been formally disseminated by EPA or USDA/FSIS. This draft guidance does not represent and should not be construed to represent EPA or USDA/FSIS policy, viewpoint, or determination. Members of the public may obtain the draft guidance from http://www.regulations.gov; or http://www.epa.gov/raf/microbial/index.htm or from Dr. Michael Broder via the contact information below.

DATES: All comments received by the docket closing date September 26, 2011 will be shared with the external peer review panel for their consideration. Comments received beyond that time may be considered by EPA and USDA/FSIS when it finalizes the document.

ADDRESSES: Submit your comments, identified by Docket ID No. EPA-HQ-ORD-2011-0532, by one of the following methods:
http://www.regulations.gov: Follow the on-line instructions for submitting comments.
E-mail: ORD.Docket@epa.gov.
Mail: ORD Docket, Environmental Protection Agency, Mailcode: 28221T, 1200 Pennsylvania Ave., NW., Washington, DC 20460.
Hand Delivery: EPA Docket Center (EPA/DC), Room 3334, EPA West Building, 1301 Constitution Avenue, NW., Washington, DC 20460, Attention Docket ID EPA-HQ-ORD-2011-0532. Deliveries are only accepted from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. Special arrangements should be made for deliveries of boxed information.

Instructions: Direct your comments to Docket ID EPA-HQ-ORD-2011-0532. EPA's policy is that all comments received will be

included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected by statute through http://www.regulations.gov or e-mail. The http://www.regulations.gov Web site is an ``anonymous access'' system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through http://www.regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

Docket: All documents in the docket are listed in the http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in www.regulations.gov or in hard copy at the ORD Docket, EPA/DC, EPA West, Room 3334, 1301 Constitution Ave., NW., Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the ORD Docket is (202) 566-1752.

[[Page 44587]]

FOR FURTHER INFORMATION CONTACT: Dr. Michael W. Broder, Office of the Science Advisor, Mail Code 8105-R, U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW., Washington, DC 20460; telephone number: (202) 564-3393; fax number: (202) 564-2070, E-mail: broder.michael@epa.gov.

SUPPLEMENTARY INFORMATION: Both EPA and USDA/FSIS have an established history of conducting human health risk assessments on chemical agents but less experience on microbial agents. EPA conducts microbial risk assessment on agents under a number of different statutes for a variety of purposes. These include both naturally occurring and genetically modified microorganisms with

the potential for environmental exposure. USDA/FSIS is charged with ensuring the safety of food from the farm to the consumer.

Microbial risk assessment entails addressing issues that are Not considered in chemical risk assessment (e.g., die off and regrowth of bacteria, effects of prior exposure and immune status). EPA, USDA/FSIS and other Federal agencies often conduct risk assessments on similar pathogens albeit in different media and under different scenarios. A common approach to conducting these assessments will foster better interaction among participating agencies leading to a more efficient and consistent process. In order to better harmonize the way that EPA conducts its assessments across programs, EPA initiated and was joined by USDA/FSIS and scientists from other Federal agencies to develop guidelines to promote greater consistency within the government and provide more transparency to stakeholders and other interested parties. This cross-agency activity has generated the draft Guideline.

This document addresses the full range of microbial risk assessment topics: Definition of the roles and responsibilities, planning and scoping, the four components of a risk assessment, and sections discussing risk management and communication. The Guideline identifies differences in issues and processes between chemical and microbial risk assessment such as secondary transmission (person to person), increases and decreases in microbial populations both in the environment and host individuals, and the role of prior exposure on disease manifestation.

Collectively this document reflects the combined experience and expertise of risk assessors and will promote a consistent approach to conducting microbial risk assessments.

Dated: July 15, 2011

Paul T. Anastas,

EPA Science Advisor.

[FR Doc. 2011-18879 Filed 7-25-11; 8:45 am] BILLING CODE 6560-50-P

George Arvanitakis
<George.Arvanitakis@hc-sc.gc.ca>
09/26/2011 08:07 PM

To Docket ORD@EPA
cc Shaunalea Savard <Shaunalea.Savard@hc-sc.gc.ca>
bcc
Subject Comments on Microbial Risk Assessment Guideline (External Review Draft), Docket ID No. EPA-HQ-ORD-2011-0532

Good evening,

On behalf of the New Substances Assessment and Control Bureau of Health Canada, please accept the following comments on the joint U.S. EPA and U.S. Dept of Agriculture Microbial Risk Assessment Guideline (External Review Draft). We hope that they are useful and lead to relevant improvements in the document:

General comments:

- Electronic versions of the guidelines may benefit from having all citations in the main text "linked" to the full citation in the References section.
- The overall readability of the document might be improved by the provision of a "key words" box at the start of each chapter. Would suggest that each chapter commence with a summary box of the key words relevant to the content of that specific chapter, taking the definitions from the glossary provided in Chapter 9.
- Mention of the 2009 NRC report is important and relevant; however, the clarity of the message may be enhanced by inclusion of the framework figure (figure 8-1).

Specific comments:

- Pg.5, line 5: it would be useful to give some examples of "pre-formed toxins" here.
- Pg.6, lines 30-35: it's not clear how these are different compared to chemical substances (for eg. it could reasonably be said that the same dose of a chemical may also result in a broad range of health outcomes or endpoints depending on individual characteristics and exposure scenarios.)
- Pg.21, lines 23-37: important distinction between "risk" assessment and "safety" assessment. Another useful distinction may be that "safety" assessments are usually conducted on microbial products where human exposure is an expected part of its use (eg. microbes in food or as vaccines, etc.). Whereas a "risk" assessment is typically conducted on products where human exposure is only incidental in their use (eg. microbes used to produce enzymes or found in cleaning products).
- Pg.44, lines 23-37: when conducting human health and environmental risk assessments under the New Substances Notification Regulations (Organisms) of the Canadian Environmental Protection Act, 1999, we encourage the use of the "polyphasic" approach for the proper identification and characterisation of a microbial strain. In other words, we encourage the use of multiple lines of evidence (morphological, biochemical, genetic, etc.) in attempting to apply a taxonomic designation to the microbial strain that is the subject of an assessment. Uncertainties at this step of the process would eventually lead to uncertainties in all steps of the process. Thus, we find that a solid ID reduces these uncertainties. Perhaps some mention of a polyphasic approach should be made here.
- Section 3, Hazard Identification and Characterisation: would suggest that history of use of the micro-organism in question be considered when trying to identify hazardous traits. As well, there is no mention of in vivo models of pathogenicity testing that can be used to evaluate the virulence of a particular micro-organism. Suggest it may be important to briefly describe the usefulness of such models in hazard identification/characterisation.
- Pg.52, section 3.7: many methodologies for identifying and taxonomically placing bacterial strains are described in the document "Guidance Document on the Use of Taxonomy in Risk Assessment of Micro-organisms: Bacteria" produced in 2003 by the OECD Harmonization of Regulatory Oversight in Biotechnology Working Group and can be found at the following weblink:

http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2003)13&doclanguage=e n
- Pg.63, section 4.1.2: it is mentioned that the “One-hit model” is the most relevant for microbial dose-response assessment. On the premise that a single microbial cell may produce illness in an individual, can there be any correlation between the severity of an infection and the initial dose?
- Pg.64, section 4.1.2: would it be possible to establish "r" values for different tissues, based on different routes of exposure (eg. "r" value for pulmonary infection based on inhalational exposures).
- Pgs 67-68: it is acknowledged that tissue colonization is difficult to measure in humans; however, there are some significant advances in *in vitro* technologies that would permit accurate, rapid, and cost-effective screening. There are numerous papers that report the use of 3D tissue culture models to study bacterial infection that may be worth considering. Although these may yet be appropriate replacements for *in vivo* trials, they are certainly good candidates for screening assessments and should be watched closely for their applicability to the regulatory context in the short term. There are many articles of relevance in the literature; the following papers useful as a starting point for discussion:
1) WERTHÉN, M., HENRIKSSON, L., JENSEN, P. Ø., STERNBERG, C., GIVSKOV, M. and BJARNSHOLT, T. (2010), An *in vitro* model of bacterial infections in wounds and other soft tissues. APMIS, 118: 156–164. doi: 10.1111/j.1600-0463.2009.02580.x
2) Carvalho R, de Sonneville J, Stockhammer OW, Savage NDL, Veneman WJ, et al. (2011) A High-Throughput Screen for Tuberculosis Progression. PLoS ONE 6(2): e16779. doi:10.1371/journal.pone.0016779
3) K. A. Birkness, M. Deslauriers, J. H. Bartlett, E. H. White, C. H. King, and F. D. Quinn An In Vitro Tissue Culture Bilayer Model To Examine Early Events in *Mycobacterium tuberculosis* Infection, Infect Immun. 1999 February; 67(2): 653–658. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC96368/ - Pg.68: Inconsistency in disease identification and reporting may also result from misdiagnosis, often due to a lack of awareness of symptoms, particularly for non-notifiable diseases. This point is made later in the report but it should also be mentioned here.
- Pg.127, section 5.4: would it be possible to assign a qualitative description (low, medium, high) to the overall likelihood of exposure at the end of a microbial risk assessment? If yes, how? Would this be useful in risk communications to the public?

Overall, these guidelines appear to be a thorough and comprehensive review of all the relevant aspects of a microbial risk assessment, and we commend both the U.S. EPA and the U.S. Dept of Agriculture for their efforts. We very much appreciate the opportunity to comment on these guidelines.

Regards,
George Arvanitakis
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Appendix D: Individual Reviewer Comments

COMMENTS SUBMITTED BY

Louis Anthony (Tony) Cox, Jr., Ph.D.

Peer Review Meeting of EPA's Draft Microbial Risk Assessment Guideline:
Pathogenic Microorganisms with Focus on Food and Water

Comments submitted by Dr. Louis Cox, Jr.

1. Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

The Q&A format is effective, at least for me. The questions asked in the table of contents are great – good scope, clearly worded, easy to understand, and addressing useful topics. (However, I think many of the answers can be improved, as discussed below.)

The overall organization reflects a fairly conventional EPA view of risk assessment: Define the scope, identify and characterize hazard, estimate exposures and exposure-response (or dose-response) relations, characterize the risks. However, for microbial risks, it is often useful to take a different approach, based on source tracking, in which genetic markers of microbes isolated from patients are used to estimate the disease fraction that could have been caused by a particular source, even when data are insufficient to model the intermediate steps of exposure and dose-response. This "backward" approach (going from the clinic back to potential sources via markers, instead of forward from the source to the exposed population, via modeled exposure pathways, to the subset who become sick, via modeled dose-response relations) provides an alternative approach to microbial risk assessment that is not in general available for chemicals (molecules are all identical, no equivalent of a genetic signature for the source) that can be especially useful when not enough knowledge and data are available to assemble a well-validated "forward" model of release, exposure, dose-response, and resulting illnesses. In these comments, I will refer to the backward approach as the "clinic-to-source" or "source-tracking" approach to microbial risk assessment. I believe that it is important enough in practice to perhaps deserve a separate new chapter, addressing questions such as "How can I estimate the risk caused by a specific microbial hazard when exposure pathways are unknown or uncertain?" and "How can I estimate the number of deaths and illnesses per person-year and per year in a population from molecular and genetic marker data, when dose-response relations are unknown?" (The brief discussion of Attribution Modeling on pp. 106-107 could provide the starting point for such an expanded discussion.)

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

The other sections and appendices seem appropriate and useful to me. (Some editing is needed in the appendices, e.g., "media" is plural, not singular.)

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

Yes, the Q&A format is suitable for multiple purposes.

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

I would add questions and answers about the source-tracking approach (see Comment 1A). Such clinic-to-source risk assessment begins by asking "How frequent is this adverse clinical effect in the population?" and ends by answering "How many of these adverse health effects per year (for population risk) and per person-year (for individual risk) could be prevented by better management of specific source (or hazard) X?"

Other comments on Chapter 1:

p. 12, lines 4 and 5: "An overarching principle for MRA in this Guideline is to provide a systematic approach to the consideration of all information… that allow a suitable examination…". Comment: How is "suitable" defined? It is usual in quantitative risk assessment *not* to consider "all" information, but only the dominant contributors that are relevant for comparing the risks from different risk management alternatives.

p. 13 and throughout: Key vague and judgmental terms such as "adequacy" (line 1 of p. 13) or "best" (line 39) or "should" (throughout) should be either defined or not used.

Page 13-14. In addition to the admirable criteria of "transparency, clarity, consistency, and reasonableness," *correctness* should also be emphasized. Many MRAs that meet the TCCR criteria suffer from the fact that they do not describe reality. What is plausible often differs sharply from what is true, in this domain. Thus, a strong emphasis on objective validation and correctness of conclusions should be added to the TCCR criteria.

p. 14, line 5 and item 4: Is this lifted from somewhere else? "Including cancer and non-cancer risks" does not seem very relevant to most MRA. In any case, the goal should be to identify and focus on dominant contributors, not all appropriate hazards.

2. Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

This chapter should be much shorter, with a clear focus on MRA (as opposed to general advice on preparing for and participating in risk assessments with multiple stakeholders and multiple levels of management).

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

Chapter 1, and other parts of the report, could benefit greatly from a tight editing job by a good technical writer. There is a lot of unnecessary prose and low-payoff sentences. (e.g., page 5, line 44, differences "can be few or many depending on… considerations." As one of many other examples, on p. 19, lines 8-

11, do we really need this report to explain that scheduling meetings can be difficult, especially if everyone wants to discuss everything simultaneously? This whole section should be condensed to at most a few lines. Obvious statements such as, "However, every risk manager may make decisions appropriate for their (sic) level in the management hierarchy" (lines 44-45), or "You should be prepared to communicate with many levels of management" (p. 20), or "Building necessary relationships with stakeholders to maintain dialogue takes considerable effort" (p. 20), or "Principal outputs from planning and scoping can include various products that are appropriate to the management plan" (p. 25) clog the report and obscure more MRA-specific guidance, and are perhaps not worth mentioning – and certainly are not worth dwelling on at length, as they are not specific to microbial risk assessment. Platitudes and empty generalities should be eliminated, such as "Depending on the risk assessment's purpose, a particular assessment approach may be employed," or "The appropriate risk assessment approach for a specific risk management problem or decision depends on the question(s) that need to be answered and the availability of data" (p. 21). This report could be greatly shortened, and made more useful, by eliminating such generic material that has little to do specifically with how to conduct a MRA.

3. Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

This chapter does not include some essential component, and does not provide usefully detailed instructions on how to plan and scope an effective MRA. It contains a great deal of general advice about social and bureaucratic aspects of risk assessment, but not much technical detail on how to do it well instead of badly. The chapter also makes some questionable assertions without proof or citations. Even the opening premise, that "Planning and scoping will help ensure that a risk assessment is relevant and well done" deserves qualification (e.g., because common mistakes in planning and scoping, such as focusing exclusively on a subset of the many strains of bacteria that are affected by a risk management intervention (such as resistant strains), can actually undermine the practical relevance and value of a MRA).

The section on formulation (p. 16) should be expanded to include undesirable effects that might inadvertently be created through risk management interventions (p. 16, item a). For example, do interventions targeted at reducing one pathogen run the risk of increasing illnesses from another, as mentioned on p. 23 (risk-risk assessments)? Such unintended consequences should be identified and addressed as part of the scope of an MRA that is intended to inform rational (consequence-driven) risk management decisions.

In some cases, a valid Conceptual Model may be unavailable, or there may be multiple plausible but distinct Conceptual Models, or the validity of a selected Conceptual Model may simply be uncertain. The guidance should address the use of multiple and uncertain Conceptual Models and model-free (e.g., source-tracking) methods as part of the formulation (p. 16).

The Analysis Plan should not be restricted to pathway-based approaches, since all important pathways may not be known with confidence, even for major food-borne illnesses such as campylobacteriosis. Risk

attribution approaches based on genetic markers are also important, and guidance should be provided on Analysis Plans for risk attribution studies.

The chapter seems to embrace, and even advocate, a model in which risk assessment is a large social activity, with many participants interacting iteratively, presumably for a substantial amount of time and budget. The authors might also provide guidance for performing a quick, sound, but limited-depth MRA (possibly in the space of a day or two, and possibly by a single analyst whose work will be checked or independently reproduced by a second analyst). Not all MRAs should require a cast of thousands, and quick, accurate calculations based on different types of data are often possible. The guidance should tell readers more about how to do such analyses.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

The needs of stakeholders (e.g., cost-effective protection of public health) can probably be better met in some cases (e.g., when causal relations are very uncertain) by modifying the approach in this chapter to emphasize multiple small, independent assessments rather than one large, carefully planned and coordinated, assessment. Section 2 extols the virtues of helping "everyone involved in the risk assessment understand how the risk assessment fits into the overall decision making process" and promoting agreement among the principle parties, with one prospective benefit being "less unanticipated controversy." However, this could be a recipe for group-think. Unanticipated controversy, properly harnessed, can be desirable when the goal is to get at the truth. As popularized in the 2011 book *Adapt*, by Tim Harford, having multiple small, independent groups try to answer a question *without* coordinating their expectations or answers may actually be a much more productive way to arrive at the right answer, even if there is less consensus along the way, than the more centralized approach advocated in Chapter 2.

Section 2.2 should address the downsides of Planning and Scoping (e.g., group-think, premature closure of rival hypotheses, ineffective pooling of what experts know) as well as its benefits, and should offer guidance for minimizing such undesired events. (A great deal is known now about how groups can avoid "decision traps," and some of this literature, from decision science and the psychology of influence and group dynamics, could be used to formulate practical guidance.)

Section 2.3 suggests that an MRA might be initiated when a hazard of concern has sufficient importance; when a risk has sufficient magnitude (probably not the right word – how about "frequency" instead?) and severity; when a situation is sufficiently urgent; or when there is enough concern about subpopulations. But these are all vague, subjective, and judgmental terms: referring to "importance," "magnitude," "urgency," and "concern" do not provide much more concrete guidance than saying "Do an MRA if you think it's worth doing.'

A more pragmatic approach might be to recognize that resources for MRA are limited, and should be spent where they are expected to do the most good. The, an agency should initiate an MRA if and only if doing so has positive value of information (VOI) and nothing more valuable can be done instead with the

same resources. This idea that costs matter in determining what to do when should probably be introduced in Section 2.3. It should be introduced again in Section 2.5.2, where it may be worth noting that "risk ranking" approaches to priority-setting are in general incompatible with cost-effective risk reduction (see Cox LA Jr. What's wrong with hazard-ranking systems? An expository note. Risk Analysis. 2009 Jul;29(7):940-8.)

Section 2.5.2 does not mention what I think of as one of the most common and useful types of MRA: a simple quantitative risk assessment (QRA), e.g., based on a number of illness-days per year caused by a pathogen in a population (or in each sub-population), multiplied by an upper bound on the fraction that might be due to a specific cause or hazard (and that might be prevented by reducing exposures to that hazard). The estimated upper bound on the attributable fraction might come from source-tracking studies. Simple QRAs are surely a type of MRA that should be mentioned. Section 2.2 also does not provide useful details on more sophisticated QRAs under "product pathway analyses" (p. 22).

The discussion of threats and vulnerabilities (pages 24-25) and CARVER needs some critical assessment and discussion. CARVER and threat-vulnerability methods have huge conceptual and practical problems (e.g., "vulnerability" is not well-defined, and "recuperability" cannot actually be coherently represented as an attribute, for most systems). It is untrue that "An effective vulnerability assessment provides a prioritized plan for mitigation measures," (p. 24) since, for example, it does not consider budget constraints (and because vulnerability has no coherent objective meaning; see e.g., Cox LA Jr. Some limitations of "Risk = Threat x Vulnerability x Consequence" for risk analysis of terrorist attacks. *Risk Analysis* 2008. Dec. 28(6):1749-1762; Brown G, Cox LA Jr. How probabilistic risk assessment can mislead terrorism risk analysts. *Risk Analysis.* 2011 Feb;31(2):196-204; Brown GG, Cox Jr LA. Making terrorism risk analysis less harmful and more useful: Another try. *Risk Analysis.* 2011 Feb;31(2):193-5.)

Pages 26-29 seem quite useful to me. If the chapter consisted of these few pages, and a condensation of the rest into a few pithy, content-full comments, the chapter as a whole might be more useful to readers who are looking for quick, practical advice.

In Section 2.6.3 (p. 30), conceptual models that do *not* "depict the movement of a hazardous agent to the host (e.g., attribution-based models, briefly mentioned later on p. 106) should also be addressed. The "movement of agent" paradigm is perhaps most familiar to EPA, but is not always the most useful one for practical MRA when pathways are not well understood.

Sections 2.6.4 and 2.6.5 do not contain much useful detail. Knowing that "The analysis plan lays out an approach to be taken" that "can act as a bridge to the risk assessment" tells me very little that is new or of direct practical value in producing an effective analysis plan.

Section 2.6.5 does not offer modern, useful frameworks for dealing with data gaps. "Ranking the importance of the data gaps" (p. 32, line 18) is not a good idea, as the effect of a data gap typically depends on what else is known (or can be discovered easily): it is sets of gaps, not individual gaps, that are important. (Also, ranking gaps does not represent the interactions among them.) Constructive frameworks that could be offered here include *conditioning* on whatever information is available, and

quantifying the value of information (VOI) as a means for deciding when to stop collecting more information and make a decision, conditioned on presently available information.

It is not clear that expert judgment should be described as "best available science" (p. 33) as opposed to "guesses that we decide to use." The track record of expert judgment in MRA exposure assessments is miserable, on the occasions when external validation has been possible. (Experts are often misinformed, show strongly correlated misperceptions, come to demonstrably incorrect consensus conclusions, etc.) Moreover, in attribution-based or clinic-to-source risk assessments, no expert judgment is needed for exposure assessments.

The expert judgment for mortality effects of PM2.5, cited on p. 34, is a great example of how expert judgment can be misused in risk assessment. Some of the key scientific uncertainties about PM2.5 and mortality have to do with whether there is any significant positive statistical association between them that remains when model uncertainty is accounted for (e.g., by Bayesian Model Averaging without linearity assumptions); whether any such positive statistical association is causal; whether it has a threshold or nadir above relevant ambient concentration levels; and whether past associations will hold in future (e.g., as age-specific heart attack rates continue to fall due to better prevention, diagnosis, and treatment). EPA's expert elicitation managed to avoid quantifying any of these key uncertainties, by assuming a Weibull uncertainty distribution that (implicitly) assigns zero probability to the possibilities that the C-R relation is not positive, is not causal, has a relevant threshold or nadir, or will change over time. There is no scientific justification for such strong conclusions; they flow (perhaps unwittingly) entirely from the ad hoc choice of a distribution that is incapable of putting positive probability mass on zero or negative values. This is assumption-driven conclusion-making, not sound scientific analysis.

In general, if expert elicitation is to be recommended as part of the guidance for attributing illnesses to pathogens (p. 35) or estimating model inputs, then past failures strongly justify a need for guidance on how the elicitation-driven results are to be validated and used to inform decision-making. Such guidance is missing from section 2.6.5.

Section 2.6.6 has some valuable ideas.

Section 2.6.7 does not capture the essence of VOI correctly. For example, the VOI framework does not imply that there should be "enough confidence in readily available information to make a decision" (p. 38, line 17). Rather, it calls for always making the best current decision one can with available information – however poor – when obtaining more information before implementing an intervention may be one of the available options, and it is assumed in evaluating alternative options now that future decisions will also always be optimized with respect to the information and options available when they are made. The claim that, "The aim of a value-of-information (VOI) analysis for the decision maker will be in its ability to determine when no more information… is economically beneficial to making a decision" is also poorly expressed. (VOI analysis might show some further information to be economically beneficial to making a decision, and yet not enough so to outweigh the costs of obtaining it.) The maximum VOI is not for "complete information" (which may be much more than anyone could or would use), but for sufficient information so that no further resolution of remaining uncertainties would change the optimal decision. Section 2.6.7 should be rewritten to give a more accurate description of VOI

and to provide some practical guidance on when and how to use it (e.g., when resolving current uncertainties would increase the expected value of optimal decisions by more than the cost of the information).

4. Chapter 3 – Hazard Identification and Hazard Characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

I like the definition of a microbial hazard as a cause of adverse effects. Identifying it as the adverse effect itself (p. 43, line 22) or as something that is associated with adverse effects (but that does not cause them) (line 24) seems to me to be confusing, and less useful.

5. Chapter 4 – Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

The crucial assertion (p. 63, line 20) that, "One-hit (or no-threshold) dose-response models are generally the most relevant" lacks citations. It is not clear when a threshold model is justified. (Goodness-of-fit tests, cited at the bottom of p. 64, generally lack power to show what dose-response models are most appropriate at low doses. J-shaped and U-shaped dose-response functions may be relevant for microorganisms that trigger host defenses. In general, the heading for section 4.1.1 ("What is the one-hit model and why is it the preferred model?") makes a presumption (that the one-hit model is in fact preferable) that is not justified by the ensuing discussion.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

A different approach is to bypass dose-response modeling in favor of using source-tracking to identify the maximum fraction of adverse health outcomes that could have been caused by a specified hazard (source of microbial risk). This approach allows the MRA to develop quantitative bounds on maximum preventable illnesses per year (or per capita-year for members of identified subpopulations) from a certain hazard (i.e., source of microbial risk), without speculating about uncertain dose-response functions. This approach is briefly mentioned under "Attribution Modeling" (p. 106), but its use in avoiding the need to specify dose-response modeling is not made clear.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

The discussion of uncertainty and variability should be expanded to include mixture distribution modeling (e.g., to detect and model the contributions from unidentified subpopulations having different dose-response relations) and Bayesian model-averaging (BMA) to deal with model uncertainty.

6. Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

The chapter on exposure assessment uses “may” so often and in such crucial contexts (e.g., “An exposure distribution may reflect the possible doses an individual could experience in, for example, one year”, p. 122; or “the complexity of this technique may preclude its widespread application,” p. 123) that clear guidance is somewhat difficult to discern.

I recommend that the discussion in Chapter 5 be expanded to explicitly address characterization of model uncertainty, heterogeneity in exposures, and robustness of exposure estimates (e.g., using BMA and model ensembles, missing-data techniques such as data-augmentation, and finite mixture distribution models). The distinction between uncertainty (including model uncertainty) and inter-individual variability in exposures can be discussed more fully and clearly in light of such technical methods and models. The fact that the same exposure distribution in the same population can elicit completely different risks (both population and individual) depending on which individuals receive which exposure levels, is not well developed in this chapter. (For example, suppose that individuals have response thresholds uniformly distributed between 0 and 1, and exposures uniformly distributed between 0 and 1. Then the expected fraction of individuals who respond can be essentially anywhere between 0 and 1, depending on which individuals receive which exposures (e.g., if individuals with thresholds of (0.01, 0.02, …, 0.99, 1) receive exposures of (0.02, 0.03,…, 1, 0.01), respectively, 99% respond; while if they receive respective doses of (1, 0.01, 0.02, …, 0.98, 0.99), 1% respond). Reducing uncertainty about the frequency distribution of exposures and/or the frequency distribution of individual exposure-response functions will not reduce uncertainty about the fraction who respond, which depends on their *joint* distribution. This type of joint analysis of uncertainty and inter-individual variability is seldom discussed in MRAs, and this chapter does little to illuminate what practitioners should do about it.)

7. Chapter 6 – Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

Equation 6.1 appears to express risk as the product of two factors. This is incorrect: as the accompanying verbal description states, risk comes from integration (or summation), not multiplication. (One typically sums or integrates over all different exposure levels and conditional probabilities of adverse effects, given exposure levels.) If one were to use a product, then correlations in the uncertain values of the quantities being multiplied would have to be modeled and used to adjust the product.

Section 6.8 appears to confuse review with validation (p. 146, line 7). An assessment may pass review because it is transparent, reasonable, plausible, etc., yet still not be valid.

8. Chapter 7 – Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

The concept of "setting an acceptable or tolerable level of risk" (p. 153, line 17) is something of a red herring. No level of health risk would be acceptable if it could be removed for fee, without sacrificing any benefits. What is "acceptable" is not risk in isolation, but only the most preferred among alternative feasible risk-cost-benefit combinations (or uncertainty sets of such combinations). Chapter 7 would benefit from a more decision-analytic approach to risk management, based on robust optimization of decisions, rather than making problematic "acceptable risk" judgments.

9. Chapter 8 – Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Framing risk communication in terms of joint problem-solving by legitimate participants, rather than only in terms of informing risk managers and the public about risk (section 8.1, p. 157), may lead to more informative and productive exchanges and participation.

Much more specific guidance specific to effective risk communication for MRAs could be given, e.g., on using diagrams that clearly show the probable consequences of different risk management actions or interventions (as in FDA's *Vibrio* MRA, which clearly shows how different chilling times and temperatures, and other interventions, would affect risk). The discussion of PR and use of public schools and public education broadcasts to "establish name recognition for the responsible agency" (p. 165) seems questionable and somewhat scary to me (based in part on discussions of misuse of Agency risk communications as propaganda, see e.g., Dan Gardner's *The Science of Fear*), and in any is not specific to MRA *per se*.

10. Overarching Issues

10A. Overall utility of the Guideline

10B. The flow and continuity of the document

10C. The consistency of the document, both in language and level of detail, across the chapters,

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors).

Covered above, especially in general comments on Chapters 1 and 2.

COMMENTS SUBMITTED BY

Darrell W. Donahue, Ph.D.

Peer Review Meeting of EPA's Draft Microbial Risk Assessment Guideline:
Pathogenic Microorganisms with Focus on Food and Water

Comments submitted by Dr. Darrell W. Donahue

Overall Reviewer Assumption: The assumption I made about reviewing this Guideline is that it would be used as a training tool for new agency employees beginning to work in the area of MRA. I read the material with that focus.

1. Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

Response: I found the Q/A format very easy to follow and user friendly. I will have some specific suggestions chapter by chapter below. Overall, I feel this is a good presentation of the basic information that an employee beginning work on MRA-type analyses would find useful.

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

Response: Both Appendix A and B are useful as supplemental material for the Guideline. One suggestion is to reformat the material in both with simple roman numeral structure to improve flow and readability.

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

Response: See above remarks.

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

2. Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

Response:

1. Overall this chapter provides a good introduction to MRA, the objectives of the Guideline and helps the reader understand the position of this work.
2. Edits/suggestions

- P.10, section 1.9. – should include here the Science and Decisions figure that describes the overall framework for Risk Analysis (Figure S-1, p. 11, NRC, 2009). Then this figure can be referred back to in the document on several occasions to keep the reader focused on the applicable framework.

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

Response: The Text Box 1.1 (General Principles of MRA) can be removed and the reader referred to the Codex (2007b) document. The reason for this text box is already made clear in the other writing around the text box. No loss of focus will occur due to this deletion. If the authors feel the text box is needed, a few summarized sentences and/or bulleted format of these principles can be offered instead.

3. Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

Response:

1. Overall this chapter does capture the primary components for planning and scoping. I will suggest some edits that will improve clarity. Some edits/suggestions are provided to improve clarity and flow.
2. Edits/suggestions:
   a. P. 15, line 30-31 – this should be updated to include the NRC 2009 reference, and then a step can be added on including "i) management options that are available".
   b. Section 2.1.1 – is out of place and breaks the flow of sections 2.1 and 2.2. Suggest moving section 2.1.1 to after section 2.2 and making it a section of its own, not a subsection.
   c. P. 17, line 10, "better informed decisions ***with stakeholder buy-in.*** – add this for succinctness.
   d. Section 2.5.1 – need to use subtitles in this section for different "depths" to make it clear that there are different depths/levels.
   e. Section 2.5.1, p. 22, Lines 23-28 – need to finish with tying these comments back into relating it to planning and scoping.
   f. Section 2.5.2 – make sure subsection titles that follow are the same as the examples list in lines 33-34, p. 22.
   g. Need a conclusion section (near p. 25, line 27) that draws the conclusion of section 2.5 – answering the "so what" question.
   h. P. 27, line 16 – be consistent with term usage (see p. 22, line 33-34).
   i. P. 29, line 25 – this reference to section 2.4 does not seem to match up, should it be "earlier in section 2.6".

j. P. 31, lines 4-9 – need to make the point that a well constructed conceptual model will enhance stakeholder's ability to better understand the scope. It might be useful to provide a simple graphic of conceptual models for the reader.

k. Consider reversing sections 2.6.4 and 2.6.5 for better readability and flow.

l. Section 2.6.6 is too long. It should be condensed into the major areas and then refer the reader to other references for more detailed information. The rationale for this condensation is to not lose the focus of the reader by presenting a long section here but rather provide the key points and then refer the reader to other references.

m. Section 2.6.7, p. 38, lines 17-22, this is a confusing section on VOI. Condense this into once sentence that focuses the reader on why VOI is important.

n. Section 2.6.8, p. 39, lines 10-14 – please reverse the order of a) and b) to make readability more clear.

o. Section 2.7, p. 40, lines 5-6 – policy choices should also be identified to the best available information during planning and scoping.

p. P. 42, bottom – a very simple and general conclusion (one paragraph if possible) should be added here to give the reader an overall summary of chap 2.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

Response: This chapter addresses the needs of the stakeholders who may read the Guideline.

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

Response: The suggestions given in the ***3A response*** above are provided to increase the overall readability of the document.

4. Chapter 3 – Hazard Identification and Hazard Characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

Response: Combining elements of HI and HC is a departure from NRC and Codex. The reader needs to be made well aware of this fact early in the chapter and that awareness should be strung throughout the document where appropriate. For the novice at MRA this combination seems to be appropriate. However, the Guideline needs to point out to the reader that this is a departure from one of the main references used here (Codex, 1999, 207a).

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

Response:

1. Combining HI and HC does prove useful in the context of MRA Guideline presented herein. In the initial section (first paragraph) the Guideline should more formally address this departure from NRC and Codex recommendations so that the reader understands the ***why this approach was taken*** better. The statement below could be used as supporting reasoning.

   > "Past risk assessment paradigms for MRA usually tie hazard characterization with dose-response. However, the workgroup felt that combining hazard identification and hazard characterization together made for an improved description of the hazard. Dose-response and its associated modeling approaches are best presented in a separate chapter."

2. Edits/suggestions:

   a. P. 45, lines 12-15, this paragraph should be moved to the first part of the chapter and along with (1) above helps with the justification of combining HI and HC.

   b. P. 45, line 16 – a short (2 sentences) section should be included prior to section 3.3 to lead the reader into the HC discussion.

   c. P. 45-46 need to reformat this itemized listing.

   d. P. 46, line 17-18, Host characterization is as important as the "omic" techniques/technologies listed here…consider reversing order of this listing.

   e. P. 56, section 3.9, line 46 – should briefly intro the idea of sensitive sub populations here.

   f. P. 58, section, 3.10. This section is really a part of section 3.9 and should be treated as such.

   g. P. 60, bottom – again, a short paragraph to conclude chap 3 is needed here.

5. Chapter 4 – Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

Response:

1. The overall D-R discussion in this chapter is at the appropriate level for novice MRA employees. The section guides the reader through what is needed to do an appropriate D-R assessment. Many of the in-depth technical details are not included here but references are provided for the reader, this is a good approach. The material is presented in a fairly logical order to walk the reader through the process. Some edits/ suggestions are provided.

2. Edits/suggestions:

   a. P. 61, section 4.1, lines 33-37 – providing a graphic to support this written section would improve the clarity of the section especially since this is an introduction.

   b. P. 62, lines 1-5 – need to provide some references here where the reader can go to find examples of outbreak data being used.

   c. P. 63, lines 38-~44 – it is useful to mention that thresholds, if they do exist, are likely host-dependent as well.

   d. Section 4.1.3 p. 65-70 – suggest using sub section numbers ex: 4.1.3.1 for introducing the various factors in this section.

   e. P. 69, lines 40-45 – should make the point that in outbreak data there is often no known "dose" level.

   f. P. 71, section 4.1.5 – add: "..each **D-R** model…

   g. Section 4.1.5 – fix obvious formatting errors.

   h. P. 72 – line 6 – add: "..rationale for the model **and logic for its selection..**"

   i. P. 74-75, Table 4.1 is a great addition to this text!

   j. P. 76-77, all equations should give chap number as well as eq…example, line 5 should state: "..(Equation 4.1)." and so on.

   k. P. 80, section 4.2.3, need to further subsection off the various criteria listed here as this is a crucial part of the modeling paradigm of MRA.

   l. P. 82, section 4.2.4 – At this point in the Guideline it would be much better to have a general discussion on uncertainty and variability followed by subsections for uncertainty and variability within the same section (say 4.2.4).

   m. P. 85, section 4.2.8 – the overarching technique that PBDRM fits into is called "Compartmental modeling (or analysis)" (CMA), and PBDRM methods are a subsection of this technique. More summary should be addressing compartmental analysis with PBDRM being an example of one type of CMA.

   n. P. 85, there should be a short 1-2 paragraph section of conclusion to this chapter.

   o. Section 4.2.1 – In the listing of types of D-R models, the use of neural networks (NN) should be addressed. While neural network modeling of microbial dose-response is not very widespread, the NN modeling technique has been used in chemical risk assessment. Below are some references that can be used to trace the use of NN models in D-R. Also, this reviewer would be happy to collaborate with you to develop this section of material if the document authors feel it is warranted.

      1. Donahue, D. W. 2005. Neural Networks: A Microbial Risk Assessment Tool. Presentation at the Society for Risk Analysis, 4-7 December, Orlando, FL.

2. Xie, BG, SX Yang, M. Karmali, AM Lammerding. 2000. A Novel Dose-Response Model for Foodborne Pathogens Using Neural Networks. SMC 2000 Conference Proceedings: 2000 IEEE International Conference on Systems, Man & Cybernetics. © IEEE.

3. Fausett, Laurene. 1994. Fundamentals of Neural Networks: Architectures, Algorithms and Applications. Prentice-Hall, Inc., New Jersey.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

Response: The coverage for D-R models in the Guideline is adequate for the stated purpose of the Guideline. Models examples presented herein are not suppose to be exhaustive, but only as peer-reviewed examples of what can be used. Maybe a stronger statement to this fact would be useful.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

Response: A section on the use of animal and/or in vitro D-R models could be added in the beginning of section 4.2 (p. 72). The general discussion could lead from types of D-R models (such as mathematical and/or animal/in vitro) to the more specific mathematical models given there. It should be noted that there are historical experimental animal data that can be used to enhance D-R modeling with appropriate references.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

Response: This has been addressed under 5A.2.l. section above.

6. Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

Response:

1. There is appropriate coverage for the information on Exposure Assessment. Some edits/suggestions are provided to improve clarity.
2. Edits/suggestions:
   a. P. 89, lines 1-6 (labeled b) – inclusion of the idea of drawing process flow diagrams (pdfs) and compartmental modeling/analysis should be addressed in this point.
   b. P. 92, lines 21-28 – should “sub-strain variability” be added to this listing?
   c. P. 93, lines 38-43 – can re-introduce the use of compartmental modeling/analysis in this section.

d. P. 94, lines 28-32 – should address ***transparency*** here.

e. P. 94, section 5.1.11 – in the Monte Carlo Analysis section, it should be stressed that transparency is paramount when deciding to take the MC approach to exposure modeling.

f. P. 95, - lines 26-28 – need reference.

g. P. 95, line 33 – Kelton is the correct reference.

h. P. 96, lines 22-25 – need to refer the reader back to ch 2 to make the planning and scoping connection.

i. P. 99 – lines 7-8 – need to reiterate the idea of ***transparency*** in the last sentence.

j. P. 99 – line 41 – include the word "..**Exposure** Assessment" (not "risk").

k. P. 100-102, section 5.2.2 – this section is one of the most confusing sections in the Guideline, it jumps around a lot and is not clear. This section needs to be re-written with the ideas that 1) you cannot enumerate all possible scenarios here and 2) focus the discussion by using the examples set forth on p. 102-103.

l. P. 106, lines 4-8 – need to reference the population list here, maybe an example of where those types of choices are being made in a risk assessment.

m. P. 107, lines 1-7 – the example presented here is a very simple and straight-forward one to get the point across. **A similar type example is needed in chap 4 for dose-response.**

n. P. 108, lines 1-2 – input-output flow is also more broadly called the "***mass balance" approach***.

o. P. 109, line 16 – insert "..between **process** steps.."

p. P 109, lines 24-25 – need to add a caution about **assuring transparency** when converting conceptual relationships to mathematical relationships.

q. P. 110, lines 5-15 – this example is not complete in its description.

r. P. 110, lines 29 – p. 111, line 4 – need to move this section AFTER p. 111, line 24 for better clarity.

s. P 110-116 – there are several issues with equation formatting that need to be addressed.

t. P. 117, section 5.2.7 – this section is of lesser importance to the overall chapter.

u. P. 118 line 16 – insert "..determined **in the planning and scoping phase** before.." (this makes the connection back to chap 2 here).

v. P. 121, lines 16-23 – need to address ***transparency*** here too.

w. P. 121-122 – need some examples provided right after p. 122, line 6 and in section 5.3.1 after line 32.

x. P. 124 lines 4-15 – need to reference this approach. Also, should these equation terms/variables be defined?

y. P. 125 lines 9-15 – need to relate back to **planning and scoping**.

z. P. 126 line 11 – need reference for Akaike criterion (An Information Criterion).

aa. P. 126 line 26 – modify as "A design of experiments technique called factorial design.." (reference: Design and Analysis of Experiments, D. Montgomery 2009).

bb. P. 128 lines 8-12 – need to address the use of showing the **baseline scenario** as a reference point for any sensitivity analysis.

cc. P. 129 – ***NOTE: there is a conclusion/summary to this chapter which is appropriate***.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

Response: This chapter covers exposure assessment material in fair detail with references for readers who want to dig further. It is not clear that additional material here would enhance the purpose of the chapter.

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

Response: Addressed in previous chapters. Refer reader back to those previous sections for this discussion.

7. Chapter 6 – Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Response:

1. The detail presented here is a fair summary of the EPA Risk Characterization Handbook and is targeted at the appropriate level for novice MRA readers. Some edits/suggestions are provided for clarity.
2. Edits/suggestions
   a. 131 line 10 – need to address transparency here.
   b. 131 lines 28-36 – need to bring "planning and scoping" back into focus here as Risk Characterization really starts in formulation of risk management considerations…in planning and scoping.
   c. 132, line 5 – change "assessment" to "characterization"

d. 133-135 – this list needs reordering to be more clear and transparent:

Old	B	A	C	D	E	F	G	H	I	J	K	L	M
New	A	B1	H	I	B	C	D	E	F	G	I	K	L

e. 136, line 37 – include ***transparency*** discussion here.

f. 137, line 41 – link ideas here back to planning and scoping.

g. 138 lines 14-16 – move "Finally…" sentence down and combine with lines 39-40.

h. p, 144 Table 6.1 – a row for Design of experiments (DoE or DoX) should be added. DoE techniques are robust and assist in determining the path of the uncertainty vector properly – in a similar way as "probabilistic uncertainty analysis" does.

i. 144. Section 6.7 – this section seems to be out of place here. Maybe place this section after section 6.8.

j. p. 146 – discussion on validation and verification. The definitions below are offered as they are the basic definitions of these ideas used in operations research/computer simulation literature.

- Verification: concerned with building the ***model right***. It is utilized in the comparison of the conceptual model to the computer representation that implements that conception. Verification asks the questions: Is the model implemented correctly in the computer? Are the input parameters and logical structure of the model correctly represented?

- Validation: concerned with building the ***right model***. It is utilized to determine that a model is an accurate representation of the real system. Validation is usually achieved through the calibration of the model, an iterative process of comparing the model to actual system behavior and using the discrepancies between the two, and the insights gained, to improve the model. This process is repeated until model accuracy is judged to be acceptable.

k. P. 147 – bottom – again an overall general conclusion paragraph would be useful here to pull risk characterization information together.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

Response: In the other chapters readers were sent to the NRC and Codex documents. Readers should be directed to the CODEX ALIMENTARIUS COMMISSION, ISSN 1020-8070, CODEX ALIMENTARIUS: Joint FAO/WHO Food Standards Programme (20th ed) for more direct explanation of risk characterization. Codex also provides reference to other risk characterization information.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

Response: The detail level is appropriate for the purpose of this document.

8. Chapter 7 – Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Response:

1. The chapter provides adequate detail for a risk assessor to understand their interaction with risk managers during the overall risk analysis process. Some edits/suggestions are provided for clarity.
2. Edits/suggestions:
   a. P. 150, lines 15-27 – need to refer back to NRC 2009 reference and chap 2 (planning and scoping) to better focus this section.
   b. P. 151, lines 15 – p. 152, line 1-5 - this section really should be a separate section labeled "organization" or something similar.
   c. P. 156, table 7.2 - **reorder** elements in the table to make more clear:

Old	1) Phy	2) Adm	3) man	4) bio
New	3) phy	1) adm	2) man	4) bio

   d. P. 156 – bottom – again an overall general conclusion paragraph would be useful here to pull risk characterization information together.

9. Chapter 8 – Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Response:

1. The chapter provides adequate detail for a risk assessor to understand what risk communication is and their role in that process. Some edits/suggestions are provided for clarity.
2. Edits/suggestions:
   a. P. 157, lines 43-44 – need to include ***transparent*** in this discussion.
   b. P. 159. Lines 14-16 – include: addressing the need to develop for **targeted (to the specific audience) communication materials.**
   c. P. 161, lines 20-21 - need to include ***transparent*** in this discussion.
   d. P. 163, line 3 – include: "..planning, **skills and practice**.."

e. P. 165 – bottom - again an overall general conclusion paragraph would be useful here to pull risk characterization information together.

10. Overarching Issues

10A. Overall utility of the Guideline

Response: Based on the assumption made during the review, the Guideline has utility for novice MRA risk assessor personnel. Additionally, it would be a good reading for many types of private and non-governmental stakeholders to obtain a basic understanding of how MRA is performed within the government.

10B. The flow and continuity of the document

Response: The flow is generally good, with the exceptions pointed out hereto. Some thought might be put into reversing chapters 4 and 5 to improve the overall continuity of the document. Overall, the use of graphics (figures, plots, etc) to enhance the reader's understanding should be considered. A few examples are pointed out herein, however, others should be considered particularly to supplement material in chapters 4, 5, and 8.

10C. The consistency of the document, both in language and level of detail, across the chapters,

Response: The consistency of both language and level is good across all chapters. There seems to be a bit more in-depth detail in chap 4 (dose-response) than others. However, for the novice MRA person this detail is warranted. It might be good to "set the stage" a bit in chap 1 to make the reader understand that this is a guide and not an exhaustive treatment of MRA. This point is made somewhat but is lost in the overall chapter. The focus of the Guideline should be to acquaint the reader with all of elements of the MRA process in food and water and not to provide an in-depth treatment of MRA. The reader should be guided to other references for more in-depth coverage.

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors).

Response: The Guideline is well written to focus on the risk assessors. It would be useful if this document (or some subset of it) could be used to educate the broader population of stakeholders, for example, NGOs, legislative technical committees, new legislative members and the like. Since MRA is a bit different than chemical risk assessment, it might be appropriate to use this Guideline as a basis for training and information for certain stakeholder groups.

COMMENTS SUBMITTED BY

Joseph N.S. Eisenberg, Ph.D.

Peer Review Meeting of EPA's Draft Microbial Risk Assessment Guideline:
Pathogenic Microorganisms with Focus on Food and Water

Comments submitted by Dr. Joseph N.S. Eisenberg

1. Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

The order as well as the topics of the chapters are appropriate for a guidelines document. The order of the chapters 2 - 6 is consistent with how most microbial risk frameworks are presented: scoping/ hazard id, dose response, exposure assessment, and risk characterization. The last two chapters broaden the discussion to issues related to risk analysis by covering risk management and communication. These chapters provide risk assessors with a sense of how risk assessment relates to the other two components of risk analysis. It is not completely clear to me why Chapter 6 should be lumped in with Chapters 7 and 8 as risk characterization is an integral part of risk assessment.

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

The inclusion of Chapter 1 is important as it provides important background and historical context for the reader. The two glossaries are nice additions. Assumptions that go into conducting risk assessments are often left unstated. It is important for risk assessors to keep these assumptions in mind when conducting risk assessments. The hazard identification questions should be a useful resource, especially for those that have limited experience conducting risk assessments.

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

Much of what is covered in this document is suitable for other scenarios. However, including a few additional examples beyond food and water may expand its applicability

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

I think that the focus on water and food works. Much of what is in this document is generic to all pathways and in fact generic to risk assessment in general. Including more text and maybe a few examples outside of food and water, however, could increase the relevance to other types of risk assessment (or would make the relevance more evident). This could be accomplished in an appendix.

2. Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

This chapter is an effective introduction to MRA. It provides definitions, historical context, rational for developing a guidelines document, and other miscellaneous background information. The section on microbes versus chemicals is a critically important section that details the ways in which microbes and chemicals are different and therefore helps to motivate the need to a specific set of guidelines for MRA. This chapter falls short in some sections in accomplishing all of it goals. For example, Section 1.6 does little in the way of answering the question about what the relationship is between the organisms (incorrectly stated as the disease in the title) and the host (or human health), rather the text simply states that there exists a relationship. Section 1.9 doesn't discuss the relationship between this guideline and others; rather it simply lists out what else is out there. Lastly, Section 1.10 is generic and not specific to MRA.

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

There are lots of examples of text that is wordy with long written out references. For example, Section 1.1 could be shortened from 15 lines to 6 lines as show here making the definition stand out and much more accessible.

Risk assessment is widely recognized as a systematic way to prepare, organize, and analyze information to help make regulatory decisions, establish programs, and prioritize research and development efforts. Here we focus on the following definition of risk assessment:

The qualitative or quantitative characterization of the potential health effects of particular substances on individuals or populations, structured to include a hazard identification and characterization, dose-response assessment, exposure assessment, and risk characterization.[1] [Foot note could contain the two references]

Section 1.3 could also be shortened by moving the 3rd and 4th paragraph to the Preface. Section 1.9 could be condensed by focusing on the relationship between this guideline with and other guidelines as well as putting references and long parenthetical comments in footnotes. Likewise Section 1.10 could be made more concise by providing a synthesis of the three cited documents rather than just listing them out.

3. Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

I think that all the major components are present at the appropriate level of detail. Most of my comments (details in 3C) are on the structure of the chapter and the inclusion of section that seem more appropriate in the Introduction chapter.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

This chapter addresses the needs of the stakeholders involved.

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

The structure of this chapter needs work. More synthesis is necessary and many sections don't seem to belong in this chapter.

Section 2.1 defines Planning and Scoping and presents EPAs Planning and Scoping in 8 steps. Then section 2.1.1 defines problem formulation as i) defining the endpoint (a term that needs to be defined), ii) developing a conceptual model, and iii) developing an analysis plan. But problem formulation is not part of the definition of Planning and Scoping as defined in the 1st paragraph of 2.1. Problem formulation is listed as the 6th step of EPA's planning and scoping (from Section 2.1). But steps 7 and 8 of EPAs planning and scoping is the same as 2 of the 3 components of problem formulation as written in Section 2.1.1. This is quite confusing as written. Then Section 2.6 describes planning and scoping in 16 steps. Conceptual models and analysis plan are two of those 16 steps as are many of the other 8 steps listed in Section 2.1. But how does problem formulation fit into planning and scoping? It is not talked about at all in this Chapter after 2.1.1. First, I would suggest deleting the 8 steps of planning and scoping in Section 2.1. This is another example of the report presenting text from other reports without contextualizing it. The text would be much more accessible if it synthesized work from other reports without listing it out verbatim. Second, I would suggest integrating problem formulation formally into the definition of planning and scoping.

Why are Sections 2.3, 2.5, and 2.8 in this chapter? Sections 2.3 and 2.5 are focused on risk assessment ('What do I consider when deciding to initiate a MRA', and 'What are examples of types of MRA') and not on planning and scoping. These sections comprise 7 pages of text and at some point I forgot that I was still in the planning and scoping chapter. These sections should be condensed and moved to the introduction. Additionally, Section 2.5.1 could be deleted without much loss of information, and the use of the term risk assessment and MRA seem to be interchangeable in these sections as well as throughout the report. Care should be given on when each is used. As with Sections 2.3 and 2.5, Section 2.8 does seem to belong in this chapter. This information also belongs in the introduction. The list presented in 2.8 should be categorized in some way as it is hard to focus on a long list without some context.

Section 2.6 is the crux of this chapter. It describes 16 components of planning and scoping. This section should be clearly laid out in parallel to the list in the box on page 25. Currently, some are described in Section 2.6 demarcated by letters, while others are given their own subsection. They are not always presented in the order of the list. Each component should be described in the order they are listed in the box with a consistent subheading. Currently, question e, i, m, n, o are not contained in the list of products, and the 'Scenario' section is out of sequence. Why not integrate Section 2.6.1 into (h)? And Sections 2.6.2, 2.6.3, and 2.6.4 should be integrated into the lettered products of 2.6. Why is 2.6.5 not considered a product (i.e., not on the list). I would suggest a smaller section on identifying data gaps as a product and then reference an appendix that discusses how to identify data gaps.

Section 2.6.6 should be clearly integrated into the description of products. This section can also be more concise and better synthesized. The first paragraph of the section is very hard to navigate and doesn't have a lot of content. The section should begin with the paragraph on p36, line 13. Then the three lists presented in the section, guidelines on data quality principles, evaluating usefulness of data quality, and basic criteria for evaluating data, should be integrated.

I don't really understand section 2.7, and it is not made clear why it belongs in this chapter.

4. Chapter 3. Hazard identification and hazard characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

I think this is an appropriate and effective way to frame hazards. Risk assessors not only need to identify the hazards but we also need to characterize them. Hazard ID is addressed in sections 3.6 (what are the pathogen categories), 3.7 (how do we detect them), and 3.8 (special issues of detection). I would move these sections up to right after 3.2. Have these sections clearly labeled Hazard ID. I think that it should be stated up front that these guidelines are using a taxonomic approach (of microorganisms) to categorize hazards and there should be a justification for this approach. Be clear that the guidelines are not focusing on other hazards such as flies that carry excreta. The last two paragraphs of Section 3.6 provide information on other sources of pathogen lists. These paragraphs should be focusing more on how these other lists compare with Table 3.1 and less on simply describing the sources. Be sure that Table 3.1 is comprehensive. A table of detection methods for Section 3.7 would be very useful.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

Providing information on hazard characterization alongside identification is quite useful. Sections 3.3, 3.4, 3.9, and 3.10 all address aspects of HC. These should be presented together and clearly labeled as HC. What is left is Section 3.5, which I think has too much detail for a MRA guideline document. This should be integrated in with HC.

5. Chapter 4. Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

The two sections in this chapter, general considerations and current practice, are in general nicely organized and accessible. One exception is the text on Bayesian analysis, which I elaborate on in 5C. Another point that should be emphasized more in the text is that the models presented in Table 4.1 are almost exclusively focused on one route of infection (ingestion) and a narrow population group (healthy 20-30 year olds). These parameter estimates are not relevant to the other routes. The use of epidemiology data to help generalize to other population groups could be addressed in more detail in this chapter.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

There are no dose-response models that I think should be included in the text. There are however a number of publications that present models of disease spread in populations that are relevant to MRA. The use of these transmission models in MRA has increased in the past 10 -15 years and should be included in Section 4.1.4. For example Zelner et al (2010) use a transmission model to examine secondary spread through households after a point source foodborne outbreak. Eisenberg et al (2005) used transmission models to analyze the 1993 *Cryptosporidium* drinking water outbreak focusing on three aspects all touched upon in Section 4.1.4: 1) disaggregating the risk associated with direct exposure to the contaminated water and subsequent secondary spread; 2) assessing the role that person – environment – person played in the outbreak, and 3) assessing the role that immunity played in the outbreak. Sheng et al (2009) provides a framework for examining Environmental Infection Transmission Systems (EITS) and could be reference as a more current motivation for the use of dynamic models focus on MRA. Eisenberg et al. (2002) provides a policy perspective for using transmission models in decision making.

Zelner J., King, A.A., Moe C.L., Eisenberg, J.N.S (2010) How Infections Propagate After Point Source Outbreaks: An Analysis of Secondary Norovirus Transmission. 21(5) Epidemiology

Sheng L., Eisenberg J.N.S., Spiknall I., Koopman J.S. (2009) Dynamics and Control of Infections Transmitted from Person to Person through the Environment. American Journal of Epidemiology doi: 10.1093/aje/kwp116.

Eisenberg J.N.S., Lei X., Hubbard A.H., Brookhart, M.A., Colford Jr. J. M. (2005) The role of disease transmission and conferred immunity in outbreaks: Analysis of the 1993 Cryptosporidium outbreak in Milwaukee. American Journal of Epidemiology 161:62-72.

Eisenberg J.N.S., Brookhart M.A., Rice G., Brown M., Colford J.M. (2002) Disease transmission models for public health decision making: analysis of epidemic and endemic conditions caused by waterborne pathogens. Environmental Health Perspectives 110(8)783-790.

Another important aspect not addressed in this section is how dose-response can be integrated into transmission models. This is addressed in the following two publications:

Eisenberg J.N.S., Scott, J., B. L., Porco T. C. (2007) Integrating public health control strategies: Balancing water sanitation, and hygiene interventions to reduce diarrheal disease burden. American Journal of Public Health May 2007; 97: 846 – 852 (PMCID: PMC1854876).

Spicknall I.H., Koopman J.S., Nicas M., Pujol J.M., Li S., Eisenberg J.N.S.* (2010) Informing Optimal Environmental Influenza Interventions: How the Host, Agent, and Environment Alter Dominant Routes of Transmission. 6(10):e1000969. PLoS Computational Biology

Finally, Section 4.2.8 discusses physiologically based dose response models. There have been a few publications in this area. Two from our group include:

Mayer B.T., Koopman J.S., Ionides E.L., Pujol J.M., Eisenberg J.N.S.* (2011) A Dynamic Dose-Response Model to Account for Exposure Patterns in Risk Assessment: A Case Study in Inhalation Anthrax. 8(57):506-17. Proceedings of the Royal Society: Interface.

Serra J.M., Eisenberg J.N.S., Haas C.N., Koopman J.S. (2009) The Effect of Ongoing Exposure Dynamics in Dose Response Relationships. 5(6): 1-12. PLoS Computational Biology.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

This is out of my field of expertise.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

Uncertainty and variability associated with dose-response models are address in Sections 4.2.1 (Bayesian Hierarchical Models), 4.2.4, and 4.2.5. The subsection on Bayesian Hierarchical Models is probably one of the least accessible sections in the report. There are lots of terms used in this section that are either not defined at all or are not clearly defined; e.g., hierarchical models, one-stage models, joint posterior distribution, Markov Chain Monte Carlo, non-informative priors, bootstrap, etc. The sentence "the predictive Bayesian dose-response function can be found by multiplying the posterior by the conditional dose-response function and integrating over the parameter space" is pretty dense. If this section is meant to be informative to non-statisticians, it will require a major rewrite. Section 4.2.4 addresses how to evaluate uncertainty in dose-response. This too is relatively inaccessible to non-statisticians. The last two paragraphs rely on an understanding of hierarchical Bayesian approaches and predictive Bayesian models from the subsection in 4.2.1. The first paragraph in 4.2.4 is confusing. First the second sentence states that 'statistical confidence limits primarily reflect variability, with some contribution from uncertainty'. Then the 4th sentence states 'some of the uncertainty can be shown by determining the confidence limits to the parameters of the dose response curves.' It is my understanding that confidence limits reflect sampling error (which in this case comes from data collection in dosing studies); and sampling error is a reflection of uncertainty.

I think it would be clearer to structure the text around two approaches to assess uncertainty due to sampling: 1) likelihood approaches that produce confidence limits; and 2) Bayesian approaches that produce posterior distribution of the parameter space.

Section 4.2.5 addresses variability in dose-response. This section is vague and not that helpful. It would be useful to talk about ways to examine variability in data. The simplest approach is through stratification; i.e., we can assess variability between isolates and strains by examining multiple dosing studies that are looking at different strains. More detail and specificity is needed.

6. Chapter 5. Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

For the most part this chapter is well written and well organized.

One section that is not that clear is 5.2.1. I am having a hard time with Table 5.1. The use of prospective and retrospective categories does not seem that useful to me. Given this is the focus of a short section on a very broad topic 'what is the purpose of the risk assessment' I would suggest aligning this section with other text in other chapters that are trying to answer the same question.

Important data sets for exposure assessment. Three data sets are missing from Section 5.2.8: 1) Shedding data. For many pathogens human shedding is an important source of pathogens in the environment (e.g., recreational waters, sewers); 2) survivorship data. There is huge literature that contains data on survivorship (see review by Boone and Gerba) in different environmental media (e.g., water and surfaces), and under different environmental conditions (e.g., temperature); and 3) data relevant to fomite exposure (e.g., transfer rates from surface to hands). I suggest a section on each. There should also be at least a paragraph on different methods for modeling survivorship.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

Fate and transport models. I think that basic fate and transport models have been neglected in this chapter. There is a huge literature on this topic that focus on transport of pathogens in water and soil. I suggest that you add at least one example on this area in 5.2.2, and consider a subsection devoted to defining what fate and transport in 5.2.4. Below is a reference from our group that provides simple fate and transport models for aerosol transport and for soil transport into groundwater.

Eisenberg J.N.S., Moore K., Soller J.A., Eisenberg D., Colford J.M. (2008) Microbial Risk Assessment Framework for Exposure to Amended Sludge Projects. Environmental Health Perspectives 116(6): 727-733.

Transmission models. Section 5.2.7 is devoted to modeling secondary transmission using transmission models. None of these references focused explicitly on the environment, a key part of MRA. Our group and others have published many articles that use transmission models in the context of environmental risks. Consider the following from out group (also mentioned above):

Sheng L., Eisenberg J.N.S., Spiknall I., Koopman J.S. (2009) Dynamics and Control of Infections Transmitted from Person to Person through the Environment. American Journal of Epidemiology doi: 10.1093/aje/kwp116.

Eisenberg J.N.S., Lei X., Hubbard A.H., Brookhart, M.A., Colford Jr. J. M. (2005) The role of disease transmission and conferred immunity in outbreaks: Analysis of the 1993 Cryptosporidium outbreak in Milwaukee. American Journal of Epidemiology 161:62-72.

Eisenberg J.N.S., Brookhart M.A., Rice G., Brown M., Colford J.M. (2002) Disease transmission models for public health decision making: analysis of epidemic and endemic conditions caused by waterborne pathogens. Environmental Health Perspectives 110(8)783-790.

Eisenberg J.N., Seto E.W., Olivieri, A.W., Spear, R.C (1996) Quantifying water pathogen risk in an epidemiological framework. Risk Analysis. 16(4):549-563.

With regards to airborne transmission models consider the following that addresses the environment (Riley et al. does not)

Spicknall I.H., Koopman J.S., Nicas M., Pujol J.M., Li S., Eisenberg J.N.S.* (2010) Informing Optimal Environmental Influenza Interventions: How the Host, Agent, and Environment Alter Dominant Routes of Transmission. 6(10):e1000969. PLoS Computational Biology

Atkinson M, Wein L (2008) Quantifying the Routes of Transmission for Pandemic Influenza. Bull Math Biol 70: 820–867.

Noakes CJ, Beggs CB, Sleigh PA, Kerr KG (2006) Modelling the Transmission of Airborne Infections in Enclosed Spaces. Epidemiol Infect 134: 1082–1091.

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

Uncertainty and variability are addressed in Section 5.1.7 and 5.1.8. The second sentence in 5.1.7 states that variability is purely the effect of chance. I don't think I agree with that statement. The variability in risk and exposure due to age are not chance events. They are quite predictable and effectively modeled/analyzed deterministically.

Sections 5.3.3 and 5.3.4 address sensitivity and uncertainty analysis.

One sensitivity analysis technique that is relevant to MRA is Regional Sensitivity analysis. This techniqe can also be used to examine uncertainty. I recommend considering adding a paragraph on this approach. Two relevant publications are:

R.C. Spear and G.M. Hornberger, Eutrophication in Peel Inlet: II. Identification of Critical Uncertainties Via Generalized Sensitivity Analysis, Water Research 14:43–49, 1980.

Eisenberg J.N., Seto E.W., Olivieri, A.W., Spear, R.C (1996) Quantifying water pathogen risk in an epidemiological framework. Risk Analysis. 16(4):549-563.

7. Chapter 6. Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

The detail presented in this chapter is sufficient. I just have a few suggestions that will enhance the utility of this chapter.

In Section 6.1, Equation 6.1 does not seem like it would be useful to a risk assessor, and I question whether it is accurate. I also would suggest deleting the sentence starting on line 40 (p 130) as it is not necessary, and I question the use of the term Hazard (rather than risk). Also, the role of dose-response seems lost in this section. I think the text starting on p41 could be deleted with little loss of content.

In Section 6.4, I disagree with the sentence starting on line 17. Risk is a probabilistic concept. Also, deterministic analysis and relative risk analysis needs to be defined.

In Section 6.5, what is the difference between qualitative and semi-quantitative assessments? These terms should be defined. I don't completely agree with the sentence starting on line 24 (p 138). Quantitative risk assessments are often conducted by using surrogate dose-response functions (e.g., rotavirus is often used to represent enteric viruses). Line 33 (p138) states that the most commonly employed classes of MRA models are static and dynamic. It would be useful to provide examples of each from the literature.

In Section 6.5.1 there are a number of issues. The first sentence states that a static model is appropriate when the central question is concerned with single exposures. Zelner et al. (see above for reference) illustrates how subsequent secondary cases from a single exposure event can be substantial. A study following 150 index cases revealed an additional 79 secondary cases that occurred within the households of the index cases. Later in this paragraph it is stated that static models are useful for analyzing situations where the effect of an intervention directed to individuals is more important. And POU remediation is used as an example. This is also not completely true. Consider the question of the risk of *Cryptosporidium* exposure to HIV+ individuals. Is it better to provide HIV+ individuals with a POU device or improve centralized treatment? The answer has to do with how strong secondary transmission is. If those without a POU device get infected, they could secondarily transmit the infection to an HIV+ individual. I think that the first paragraph could be simplified by simply stating that a static model is appropriate when secondary transmission rates are negligible, which is true for a number of zoonotic pathogens. This is basically stated in the second paragraph, but may be lost after reading the content of the first paragraph. The third paragraph in this section seems like it may confuse the reader. New concepts are used (e.g., chemical risk assessment-based models, estimate risk at the individual level, concept of independence) to basically say the same thing as is stated in the first paragraph. Also, the last sentence of this section is not correct. Secondary transmission can increase or decrease the level of infection relative to a specific exposure. It

can increase the level through amplification, but can decrease the level because people get infected through other exposures routes making the exposure of interest less important.

In Section 6.5.2 line 23 (p140) the sentence starts with 'In this form' implying that this is true for deterministic but not stochastic models. This is not true. Also, the sentence beginning on line 20 (P141) is not exactly true. Not all stochastic model examine probabilities at the individual level. Compartmental stochastic models lump individuals into a group just like deterministic compartmental models. Only individual based stochastic models examine probabilities at the individual level.

In Section 6.8 the text wavers a bit on what validation is. I don't completely understand the second sentence in the first paragraph. How does one validate a conceptual or mathematical model? For the mathematical model, is this referring to code validation? I think that it is important to say upfront that risk assessments can never be validated in the true sense of using independent data to validate the estimate. A risk assessment is generally looking at levels of risk that are not measureable. I would suggest rewriting this section. Phrases like 'sanction the validity of the mechanics of an assessment model' (line27, p 146) should be deleted. And the 'the following examples illustrate MRA model validations (line 44 p146) should be rephrased. These examples do not illustrate model validation in any sense of the word. The following article provides an excellent overview of verification and validation and introduces the concept of confirmation.

Science 4 February 1994: Vol. 263 no. 5147 pp. 641-646 DOI: 10.1126/science.263.5147.641.
Verification, Validation, and Confirmation of Numerical Models in the Earth Sciences. Naomi Oreskes, Kristin Shrader-Frechette and Kenneth Belitz.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

Mentioned in 7A.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

I think that in general it does a good job in synthesizing chapters 3-5.

8. Chapter 7. Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

The amount of information provided on risk management is appropriate for this guidelines document. There are a number of ways to help make this chapter more concise.

In 7.1, again the text relies on providing information and quotes from other reports. This could be tightened up and synthesized better. For example, the section begins with two NRC definitions of risk management from 1983 and 1996. It goes on to say that these NRC reports focused on risk management associated with a single risk assessment. Then there are two lists from the presidential commission and Haimes (2004) that broaden risk management to address multiple risks. This section could stick with the 1996 NRC definition that focuses on single risk assessment and then a synthesized list illustrating a process that focuses on multiple risk assessment. The classes of risk management then follow. The Codex principles could be deleted with little loss of content.

In 7.2 in it not clear why the 5th paragraph describing what a lead risk assessor does belongs in a section on how risk managers can be involved in risk assessment.

In 7.4 it is not clear why the paragraph, beginning on line 15 (p 153), that discusses risk managers role in determining acceptable level of risk is in a section on inputs need from risk assessment. This paragraph could easily go into the reduced Section 7.1.

9. Chapter 8. Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

The amount of information provided on risk management is appropriate for this guidelines document. This chapter is well written and organized. I have nothing specific to add.

10. Overarching Issues

10A. Overall utility of the Guideline

This is an excellent document to have as a resource for risk assessors

10B. The flow and continuity of the document

I think that there are some organizational issues that should be addressed. I have provided specifics in my comments above. Also, as I mentioned throughout, the text often relies on passive description of text from other reports. More synthesis would help make the document easier to read and would make it shorter. After all, this report is a guideline document and therefore should be more active in its guidance. Care should be given in assessing why each section is present, whether all the material in the section is relevant to that section, and where that section comes in the context of the chapter. I again have provided suggestions in my comments above.

10C. The consistency of the document, both in language and level of detail, across the chapters

There is repetition of certain topics in the chapters such and uncertainty and variability. The level of detail varies across those chapters. More care should be taken to make sure these paragraphs are presenting complementary material while still acknowledging that the other sections exist.

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors)

While focusing on risk assessors this document is applicable to stakeholders as well.

COMMENTS SUBMITTED BY

Jeffrey K. Griffiths, MD, M.P.H.

Peer Review Meeting of EPA's Draft Microbial Risk Assessment Guideline:
Pathogenic Microorganisms with Focus on Food and Water

Comments submitted by Dr. Jeffrey K. Griffiths

1. Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

The overall format is clearly laid out in a coherent and hierarchical fashion. Subsection headings such as "2.6 What is Discussed During Planning and Scoping and What Products Emerge?" fits within a questioning titling for subheadings which is consistently used except for Chapter headings, where larger content areas are grouped.

I found this format easy to use, and it was easy to identify topical areas and commonly encountered issues.

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

Glossary. Useful. In a living document electronic format this has scope for enlargement. *** There are some terms, such as HAACP, which are found in the abbreviations, found in the list of identification questions, but not defined in the glossary. There should be a mapping of these so that the glossary explains all such terms.

Abbreviations. Useful. One could have abbreviations in one long list (current version) or by groupings such as organizations, pathogens, etc. but I favor the long list so that the reader can simply find the abbreviation by alphabetical rank order.

References. No substantive comment. One wonders if the reference list could be expanded to include references which do not require a subscription service to access, e.g., indicate which are Open Source.

Appendix A, **Example Assumptions,** was valuable. Noticeably, some assumptions had interpretive comments after the **bolded assumption** but others did not; for example:

> **A mathematical model is assumed to adequately represent complex biological phenomenon and ecological relationships**

had no interpretative comments, although it is clearly best to be humble about assertions that complex phenomena are (1) completely understood and (2) all of the relationships are known and (3) therefore can be represented mathematically. Perhaps this Appendix could be rendered more consistent with a landscape

view table with the assumption on the left, and on the right reasons for making the assumption, and potential caveats.

The division into assumptions labeled as general, host, pathogen, environment, exposure scenario is reasonable and allows for expansion in a living document framework.

Appendix B, Hazard Identification Questions

Opportunities exist to make this list of queries more useful without substantial expansion. For example, questions are asked about manifestations of disease, with the section *Questions concerning the Host*, and the chronic manifestations (question #26) are the first time it is clear that the host manifestations can be expected to have both acute and potentially chronic manifestations.

****Many of the questions such as "What is the incubation period?" [Question 29, page B-2 line 39] could have a section reference or references, where the importance of this question is explained in the document. To be clear, by this I mean that after the question, portions of the document pertaining to the question are cited by stating something like, "see Section 2.3.4.5 and Section 34.2 for rationale."

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

The major concern I have is the use of jargon which is not easily understood. There is some heterogeneity of clarity and the apparent assumption that the reader is, or is not, already somewhat conversant with the topic, biological concepts, and mathematical tools.

On page 4, line 8, the word "media" is used for (one assumes) food, drinking water, and surface water, and "matrices" are then used in the next line. The first time a technical term is used it should probably be defined, or at a minimum be entered into the glossary. Media to most people relates to television, radio, and so on.

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

These are provided above with a rationale.

2. Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

The first 5 pages of this chapter provide a good introduction to the topic. In the general comments a few items have already been mentioned which could improve the reader's ability to understand it, e.g., the comments about media and matrices.

The Preface (page viii) alluded to long-term consequences, yet in this chapter the statement is made that MRA typically only looks at acute but not chronic sequelae (for example page 7, lines 37-41; kudos to the writers here, because the term "chronic" is defined!).

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

I see little that is superfluous. Indeed, this chapter is a critical one, and I was surprised that shortening it was the question for 2B. Section 1.9 could be moved to the Preface.

*** One aspect is missing: Urgency. Sometimes an MRA is urgently needed (page 17, chapter 2, line 27) because of an emergent risk to the population. This is a major difference between microbial and chemical contaminants – not that emergent risks are not urgently needed for chemicals, but rather that microbial pathogens inherently are more likely to be involved in epidemics, etc. Gieseke's book on infectious diseases epidemiology notes this as a classic difference between chemical and microbial agents.

In the section on differences between microbes and chemicals, there is a marvelous opportunity to provide concrete, commonly understood examples for why these important differences are important.

Microbial growth and death – The obvious but not included sentence at the end is, "These toxins are the cause of food poisoning." Otherwise the explanation is unlikely to be connected by the reader to the *reason why even dead organisms are of concern to public health.*

Host immunity and susceptibility. This paragraph discusses susceptibility due to immunity, with some reasons for enhanced susceptibility *again linked to immunity* at the end. The reasons for enhanced host susceptibility unrelated to immunity are not discussed. One could consider adding, concomitant other illnesses, medications, etc since these (in the context of the US) are likely more common than malnutrition, for example. Some reasons for increased susceptibility, for example, could include the use of medications which decrease stomach acid production, which as a negative consequence eliminates a barrier to many bacterial pathogens by reducing the infectious dose. The use of this medication is not related to immunity; nor is it a factor which is also common to chemical risk assessment. Should there be a section of bullet on microbial susceptibility unrelated to immunity? I think so.

Diversity of health endpoints. What is discussed is the spectrum of symptoms as classified along the continuum from asymptomatic to lethal. What is not discussed is that the diversity of health endpoints ALSO relates to which organ systems are involved, and that the diversity includes acute and chronic effects. Enterovirus infection can be asymptomatic or severe, but also cause diarrhea or cause viral meningitis. Infection with *Campylobacter* can be asymptomatic or mild, acute, and have chronic effects such as arthritis, inflammatory bowel disease, or Guillain-Barré syndrome paralysis. These different syndromes illustrate the diversity of health endpoints unrelated to severity. Thus a different axis or different axes could be at least mentioned here.

Genetic Diversity…. Stating that organisms can change and evolve is clear; the use of the wording "allelic ratios in a population can change significantly within a few generations" is jargon no one except a person learned in genetics or microbiology will understand.

Secondary spread …. This is such a critical difference! In infectious diseases epidemiology the crucial point is that a person with the disease or outcome of interest becomes a source of spread to others, unlike the epidemiology of chemical exposures. Gieseke's short book on infectious diseases epidemiology states this is really a seminal difference. While the whole concept of reproductive rate (R_0) is too complex for this paragraph, stating that epidemics may occur when secondary spread allows more than one person to be infected by the first person affected gives a common sense anchor for the reader not trained in epidemiology or microbiology. "Estimates for secondary spread of malaria exceed 50 secondary cases for each primary case, and for measles about 15 to 1" could help to bring this into focus.

Heterogenous spatial distribution… This may be a good place to introduce the use of the word "matrix" which appears throughout the text and needs more contextual explanation.

Single exposure…. Lines 40-42 stating that longer-term risks for pathogen exposure are not typically considered for MRA gives the possible impression that they *should* not be typically considered.

I object to this wording for the following reasons:

If the MRA is for acute diarrhea after exposure to a pathogen in food, fine; but if it for health effects after exposure to a pathogen, then it is not okay. Stating that longer-term sequelae have not historically been done is true – something many people believe to be a flaw in the historical applications of MRA for some pathogens - and so also stating that this leads to under-estimates of the true health burden because of the exclusion of these provides a more balanced view. Some whom use this document may interpret sentences just as I have outlined in an attempt to do what is "typically" done.

Furthermore, page 12, in Text Box 1.1 General Principles of MRA, point 27, states that "Acute, chronic (including long-term), cumulative and/or combined adverse health effects should be taken into account in carrying out risk assessment, where relevant." The paragraph following the box (line 3, page 12) states "An overarching principle for this MRA is to provide… a systematic approach to the inclusion of all information…."

This guide will be used by many people, and so it is important to note where MRAs in the past have, with the benefit of hindsight, not included what we now know to be important.

Wide range of microbial response to interventions… No comments.

Detection method sensitivity Agree with the caveat that the limitation cited (detection of one organism per 1,000 liters) is not *currently* reliable. There are many groups working on concentration of viable organisms from large volumes of water, and perhaps the reader should be alerted that detection method sensitivity is in general improving and likely to lead to a changed understanding for rare organisms.

Again, if this is a living document for multiple audiences, then in this critical introduction I would be sure to note that methods are changing!

Population, community, …. Dynamics. The point to this paragraph should be that the naïve reader is cautioned; cautioned to try to understand what is known about these dynamics when conducting an MRA for a specific pathogen, since sometimes the dynamics are well known, and otherwise not.

Routes of exposure. One element lacking is the fact that some organisms can be transmitted via one route of exposure and then transmitted to secondary hosts via a different route, such as oral ingestion for a virus leading to spread by respiratory droplets, fomites, etc.

***** in general, one aspect not really enunciated is that for many microbes, the likely biological routes of infection and the forms of disease are understood; whereas for chemicals, the reverse is true as the totality of health effects is often unknown. Conversely, detection of chemicals is a given media is far less of a stumbling block, but for microbial agents detection can be difficult (if scarcely present) or if it is non-culturable. Opposites.**

Balance of chapter – no comments except perhaps section 1.9 moving to Preface.

3. Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

This is a very well written chapter and does capture the essential elements for scoping. One can see that one agency or another might add more information to one section or another, but it is well written. This chapter addresses the needs of the risk assessor and his/her manager, but I am unclear that the *role* of the interested parties and their inputs is adequately reflected in section 2.4 except in the paragraph on page 20, lines 4 to 10.

Section 2.5.2 e, MRA types – one element not discussed or mentioned is that risk may change over time because of climate change. For example, the CDC is now seeing more cases of *Acanthamoeba* infections being reported, and there is concern that central nervous system disease from this pathogen, which has been quite rare, is on a real increase. Thus, within the examples, it seems to me that the magnitude of health risk due to changes over time can be incorporated into the simulations and modeling performed as part of the MRA.

Section 2.6:

*The word "taxon" (line 33, page 26) is defined here as genus, species, biovar – and in subsequent chapters, referred to without definition. Taxon is jargon and the public (and most professionals) are familiar with the words species, genus, family, and possibly biovar – this should be included in the glossary and in subsequent chapters, the word taxon should be defined again as one cannot assume a reader will read with all chapters or modules, or read them with the same level of attention.

Section h, page 27, line 27: How do I know what questions the risk assessment needs to answer? What is stated is that this is written down and iteratively discussed between the team and the managers. Where is the public or interested parties? Does one assume the risk managers are in communication with them? Ummm. I would say that it should be explicitly stated that the questions to be answered have to be informed by the public or interested parties.

Section 2.6.5. is just brilliant in delineating the tensions which are *inevitable* when data is incomplete, expert opinion an option, and so forth.

Section 2.6.6. discusses what good quality is. I have seen a lot of data excluded from consideration in science because of minor flaws or issues, which may lead to uninformed or limited assessments. For example, if the quality of data is not great – but consistently shows risk or an absence of risk – then the assessor should probably note that the data available is not of top standard but there is a consistent pattern of whatever it shows. In my experience, many public policy decisions have to be made in the absence of perfect knowledge and have to be informed by MRAs (or their equivalents) which have clear data gaps.

4. Chapter 3 – Hazard Identification and Hazard Characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

There is a lot of confusion even amongst scientists about identification versus hazard characterization as these have specific jargonist meanings to regulatory agencies. The definitions offered (lines 5-11, page 43) and section 3.2 (pages 44-45) confirm that even in this document they bleed together. One identifies the hazard and characterizes its nature. The WHO/FAO framework, alas, is far more intuitive with the inclusion of the dose-response relationship as hazard characterization. This is an example of how the adoption of the HI/HC differentiation as being separable from the dose-response relationship is somewhat arbitrary and continues a jargonistic approach. The exclusion of dose-response knowledge from the hazard characterization as it is part of the modeling is an example of what feels like a false boundary. Anyone knows a lot of a pathogen is worse for you than a little of it in terms of getting sick from it. If identifying and characterizing the hazard is "(1) this pathogen is in my water and (2) there is a lot of this pathogen in my water" then even before modeling exercises, the element of dose is present! The way characterization is dealt with is to say the pathogen is known to be pathogenic, and is {more or less} pathogenic.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

Since I don't agree with excluding dose-response from hazard characterization I cannot provide a rationale for "enhancing the utility of this approach." The only thing I can say is that to avoid confusion, state that the EPA/USDA approach puts the qualitative aspects of hazard characterization in a different bin that the quantitative characterization.

If the working group wish to exclude dose-response from characterization, they should just note that different agencies, countries, institutions use different jargon for this and I would suggest a simple table be devised to expand on lines 12-15 on page 45. This table would list activities or information, and what the rubric is in different kinds of organizations.

Other notes:

Page 44, lines 23-29, I originally had to re-read a number of times, as I did for 31-37. Would state what a taxon is since this is jargon and most people understand the words isolate or isovar, species, genus, family, etc. but fewer use the word taxon.

Page 45, Invasiveness, section 3.3, lines 24-25 – Invasiveness is defined as ability to migrate through the extracellular matrix. This is wrong. It also includes the capacity to invade cells. On the next page (section 3.4), in the paragraph starting on page 35, there is an accurate definition of invasiveness.

Page 45, section 3.3 Genetic drift – changes in the frequency of alleles due to <u>random sampling</u> – this is not helpful as it suggests it is related to what some observer finds when sampling a population, not a drift occurring because of a by-chance increase or decrease in the frequency of a genetic trait over time because of random fluctuation or inheritance. This "random sampling" definition is actually the lead line of the Wikipedia definition for genetic drift. … and in specific, the word "sampling" here is highly jargonistic and very unlikely to be understood. Even one or two sentences would be helpful in avoiding misinterpretation of this language. {another example of use of jargon}.

Page 48, line 12, "Techniques of biotechnology take advantage of these mechanisms…" might best read, "Scientists take advantage of these mechanisms to precisely transfer…" Persons take advantage of the methods through biotechnology, the methods do not act on their own. Awkward.

Page 48 lines 37-38 – define superantigens, quorum sensing if you mention them here, and include in the glossary.

Page 51, Table 3.1 –

May wish to have common agents at the top of the list and rare agents, or potential agents, at the bottom within each category to give the reader a *ranking* of occurrence.

Franciscella tularensis is the first bacterium under foodborne and waterborne microorganisms but is a rare infection in the US. Similar comment for *Brucella suis*. I would be sure to add Shigella. Under viruses, add enteroviruses.

Page 52. This section lacks a really critical piece which is that an organism usually has to be known to be a pathogen, and have an easy method for detection (such as culture) for it to be frequently detected through surveillance or epidemiology. This is alluded to but the *practical thing to plant in the reader's mind* is that many organisms which cause human disease have to be detected by molecular methods like PCR. PCR is a widely understood acronym and it is not used. Secondly, there are now techniques to concentrate drinking water so that detection is enhanced. It is almost unbelievable this aspect is not discussed. There are zillions of papers on the need to concentrate source water so that the detection capacities are enhanced (instead of 1 pathogen in 1000 L, it is 1 pathogen in 10cc).

Section 3.9 – introduction; also section 3.10 - Suggest that the fact that ALL people pass through infancy and many through pregnancy and old age means that ALL people are "more susceptible" at one time or another. This is clearly stated on lines 11 and 12, page 83, section 4.2.6.; and in Chapter 6, section 6.2 on page 133 lines 33-37.

5. Chapter 4 – Dose-Response Assessment

I am not a mathematical modeler but rather work with modelers in my own work, and therefore am probably a good example of a potential reader who has to understand the modeling even if I am not the person who conducts it.

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

The discussion is excellent. I would supplement the models with representative graphs which illustrate the functions described in this chapter (see 5D below).

In this chapter, I would note and cross-reference the descriptions of sensitive populations on page 105, chapter 5.2.3, and the description of host factors to consider (3.9, pages 56-58). There is substantial merit in having each chapter – each module – stand on its own, and each of these descriptions have their integrity and add to the logic and flow of each chapter. I do NOT recommend dumbing down the chapters by referring to a single list of compiled sensitive populations referenced somewhere or another in the MRA. The fact that sensitive subpopulations are identified during multiple stages of the MRA process is a strength and inherent to the process.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

Not aware of any others; may be outside my expertise.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

This question, on other accepted animal or *in vitro* dose-response protocols, is actually answerable with the observation that there are many, many models for infection which exist. While I am familiar with (and have worked with) a number of them relating to some bacteria and protozoa, and can volunteer several examples, my own expertise does not extend to a number of the viral pathogens or some of the bacteria. Given the broad scope (hundreds of potential known pathogens, possibly multiple models for each) answering this question in terms of other models could occupy several weeks of my time. My suggestion is that a literature review and assembly of models be conducted, and a first version of this could be done by graduate students in microbiology or a similar field. There are recognized experts in dose-response animal models and dose-response *in vitro* models whom could then be engaged if necessary. This is a really important question and information along these lines would be useful to a broad audience.

In general, *in vitro* models vary enormously as to their applicability; animal models less so, but still differ from humans; and other than humans, the most 'obviously' applicable are probably primate models. At this juncture there is less and less primate modeling being done for a number of reasons (animal rights, costs, others).

For invasive bacteria, and *Cryptosproridium,* the gnotobiotic piglet model has proven quite useful. It has been used to study dose-response effects for *Cryptosporidium, Campylobactger, Shigella,* rotavirus, , *Helicobacter pylori, Salmonella spp.*, and many *E. coli* types (enterotoxigenic; enteroaggregative; enterohemorrhagic such as O157:H7; enteropathogenic). Furthermore, there are infectious agents of swine – such as caliciviruses – which are very similar to human caliciviruses, and provide examples of animal-adapted pathogens (similar to the human) which could be used for dose-response experiments.

The rationale for the inclusion of other models, especially those from animal experimentation, is that they are informative as to the nature of the likely best models. The piglet model outlined above is also useful because of the similarities between the immune systems of swine and humans.

Some animal models may not be helpful when issues such as infective dose, or range / spectrum of syndromes, are considered. *In vitro* experiments are often chosen to study mechanisms of entry rather than infectious dose, as cell lines may in fact be chosen because they are particularly permissive to the infectious agent in question. Thus for this reason, as well as others, animal models are generally superior to, or more directly informative than, *in vitro* models.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

This chapter is in my view a model of clarity and could be published as a review of modeling.

My major comment is that the chapter could benefit from **illustrations** as well as easily **downloadable software** for the viewer. Since the intent is for this document to be useful to a wide audience, and since most people come to understand complex topics through a variety of means – reading, lectures, visual displays, tactile interactions – having illustrations comparing different distributions, and perhaps some infectious dose (ID_{50}) curves would be quite useful. The discussion regarding dose, for example, could be illustrated by the latter.

The use of illustrations in this chapter would or could be similar to that used in the subsequent chapter e.g., on page 97, Figure 5.1.

6. Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

This discussion is very well written and complemented by the many examples in the text. I suggest that some of the terms – such as "direct" exposure routes on page 90, line 19 – and from prior chapters be looked at for harmony, since "dermal" is frequently used for direct skin exposure, and similarly, "inhalation" (line 15, page 90) have added to it wording such as "also called respiratory" which is used in the infectious diseases and transmission literature. [This comment equally holds for many of the prior chapters. One of the fun things about this document is the clearly different yet highly relevant and complementary backgrounds of the authors].

On page 105, section 5.2.3., there are a list of sensitive populations and life stages to consider. It is good they are mentioned and I would cross-reference this to the discussions in earlier chapters, noting that sensitive subpopulations are considered in multiple stages of microbial risk analysis.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

Comment 1. This comment is offered to complement the discussion in 5.2.7, page 117 and also applies to a number of other chapters where the modeling of infection in the population occurs. Sophisticated models for infectious diseases in a population go beyond some of the models mentioned in the MRA draft. For example, the author(s) of this chapter mentioned Anderson & May as intellectual leaders as well as Hethcote (lines 22, 23 page 117). For some pathogens, immunity is only partial, or wanes, even after infection, and so the concept of susceptible and immune are almost idealized states which fit some infectious diseases (hepatitis A, for example) but not others (bacterial toxins, many protozoa). I think a diagram or two of disease transmission models would be helpful to the readers of the MRA Guidelines to help them to visually understand the states, transitions from one state to another, and the importance of new persons coming into a community (e.g., through birth) and persons leaving (migration, death). An example of such a figure is Figure 6.2, on page 141. This figure is quite helpful; what has just been mentioned, the addition of new susceptibles (through birth or migration) would be a new box with an

arrow facing into the susceptible population. Removal (death or out-migration) would be an outcome from the diseased or post-infection box.

Then in reflecting through the above comment on this chapter (as well as the others), I believe a chapter on the basics of infectious diseases epidemiology may be of benefit for the Guide. I will append this comment to my general comments later on. Having taught and communicated the essentials of this topic for several decades, my opinion is that it could aid the MRA Guideline in that issues such as surveillance (which affects population assessments of disease), the role of immunity in transmission, carrier states and symptomatic disease, and differences with the epidemiology of chemical exposure could be synthesized. For example, the section 5.2.8 (What Data Can I Use in an Exposure Assessment?) would be informed by this addition.

Comment 2. The issue of seasonality and temporality, and the influence of the environment (e.g., temperature, rainfall) are not discussed in this chapter. Clearly the risk of food borne *Campylobacter* is higher during the seasonal summer in the US than during the winter, because of food handling issues and growth of the bacteria in the warmer environment; and similarly, there is a temporal issue relating to the presence of pathogenic protozoa in source waters as well. I recommend they be added.

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

See above comment on seasonality and temporality above, as they contribute to variability (and sometimes uncertainty).

7. Chapter 6 – Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Comment: this particular discussion might well discuss successful microbial risk assessments – and why, giving reasons drawing upon Chapters 3-5 – and ones that were not successful, again with detail as to why. This form of review is really important and examples would successful and non-successful work would help readers to understand what makes an integrated risk assessment a real benefit – or how fatal flaws can be avoided. This may be uncomfortable to do, especially if the fatal flaws example stems from one's own work or that of institutional colleagues – but there is no substitute for this in the real world.

The chapter is fluently written and information rich. The objectives which are outlined in the introductory portions of the chapter neatly match the goals and objectives of risk assessment laid out in the prior sections of the MRA Guideline, even preceding Chapters 3-5.

On page 134, section 6.2, **Variability** (lines 5-14) would add "such as seasonal differences" as an example which affect variation in the environment (lines 8-9). In this same section I am unclear which

place this might go, but in either **uncertainty** or **bias and perspective** would consider adding something about the uncertainties about population estimates of a disease based upon surveillance reporting. Many agencies in the US, in my experience, have treated state or national reported disease as being equivalent to the population burden, perhaps because one cannot be criticized for the using a "authoritative" source even if the source notes that the reporting is an underestimate of true disease burden. In Chapters 4 and 5 there is mention of this and the need to add a correctional factor, and it is not reflected in this set of bullets. Having said this, the discussion of uncertainty and sensitivity in section 6.6 on page 142 is quite balanced overall.

This is one of the first time DALYs and QALYs are introduced, which were not discussed in prior chapters to any significant extent. Thus it is hard to look at this section in the lens of 7C, adequate detail used from Chapters 3-5. The discussion regarding the controversies is only noted in one paragraph, on page 145, and issues around the discounting of future disease (classic economic approach) versus the avoidance of disease – " I would do anything to avoid my children or grandchildren from having this, so don't discount the consequences if they occur in the future" - are not delineated at all.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

In the introduction (page 130) good risk characterization materials from the WHO/FAO should also be cited.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

Yes.

8. Chapter 7 – Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Given the restricted goals of this chapter – to be an introduction, and not comprehensive – I found this a good overview. In the list of approaches given in section7.4 (pages 152-154, I was unclear how the general guidance that no chemical should cause cancer in more than 1 in a million people exposed to it, or that drinking water contaminants should not cause illness in more than 1 person in 10,000, would be categorized.

Successful examples of risk management might be included – especially cases where prescient mixed qualitative/quantitative work led to decreases in exposures and were later reinforced by subsequent data.

There is a crucial sentence which leads the paragraph on line 4, page 153, "Risk managers make decisions under uncertainty." When there is certainty, then the need for risk assessment is mitigated since the public

policy implications are obvious. It is a crucial function of governmental and independent organizations to wrestle with questions around which there is uncertainty, and to do the best job possible to estimate risks given the information at hand. I think this point could be made earlier in the chapter. In most of the work I have been involved with advising governmental groups over the past 15 years, it has been these areas where uncertainty lies where most risk assessment activities occur.

9. Chapter 8 – Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

In section 8.4, page 159, two examples are given (lines 10-12) about different stakeholders – technical experts and the lay public. Most risk communication experts, and modern communication theory, anticipate the identification of multiple (many more than 2) target audiences for communication. The risk assessor may be asked to develop materials which could be used for communications with these multiple groups. They could include:

- Technical experts – this could include microbiologists, mathematical modelers, experimental scientists, water treatment or food processing mavens, epidemiologists, - separate audiences.
- Lay public: rate payers, community activists, activists focused on a particular disease caused or associated with the microbial risk (such as advocates for children, or persons with HIV/AIDS), environmentalists, animal rights advocates, etc. – again all members of the public, but separable.
- Persons with financial or professional interests in either the status quo, or with the adoption of new technologies or techniques which may be eventually preferred or mandated because of the risk assessment.
- Governmental officials at the local, state, and national level – and administrators who will have to enforce or monitor actions taken as a result of the assessment.

This list in my view may help to explode the view that the public are monolithic, and explain the diversity of materials which may be needed by risk managers.

In section 8.12 there is much wisdom (pages 163-164) around the need to be honest, and the need to state when facts are not yet known – sometimes being demanded by the public during an emergency – and will be communicated as soon as more information is available. I believe that stating that false reassurance is a flaw. Examples which can be given might include public relations disasters and successes. People trust authorities who are honest with them and admit when they do not know something, but will share everything they find out when it is known. They distrust authorities who withhold information. Much of this is captured in the document yet the chapter could be strengthened by making this clear set of statements.

10. Overarching Issues

10A. Overall utility of the Guideline

I believe this document will be useful to its intended audience. Its utility will be enhanced by the (downloadable, or provision on CD) availability of other documents, software packages including mathematical tools which may be able to readily use information entered into commonly used databases, research papers, and reports for the reader who wishes to pursue additional information / depth of knowledge relating to a specific module or chapter.

10B. The flow and continuity of the document

In general the document is clear and the flow within chapters is logical. I have noted places where this could be improved.

10C. The consistency of the document, both in language and level of detail, across the chapters

There are some terms which are jargonistic which are used in the document which decrease clarity, or which are so associated in the minds of many readers in a different direction that they should be either changed, or carefully explained. These have been identified.

The desired level of detail varies between chapters, with for example chapters 7 and 8 intentionally having less detail in them. I have found a need for illustrations, and for illustrative examples, in a number of the chapters and identified some places where they might be useful. I would suggest that whenever a process or mathematical concept is described, a visual representation be considered since people learn in a variety of fashions.

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors)

This document has the potential to be a “go-to” document with broad appeal to many stakeholder groups IF jargon is minimized, examples are given, and visual representation of complex subjects are provided. On page 14 of my comments I gave a list of possible communication target stakeholder groups, and my sense is that most if not all of them would be well served by this document.

COMMENTS SUBMITTED BY

Mark W. LeChevallier, Ph.D.

Peer Review Meeting of EPA's Draft Microbial Risk Assessment Guideline:
Pathogenic Microorganisms with Focus on Food and Water

Comments submitted by Dr. Mark W. LeChevallier

1. Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

Overall, the Guideline is well written, easy to read, and informative. The division of the document into the eight chapters provides a logical and easy to follow guide. The question and answer writing style is easy to follow and allows one with a cursory or specific interest to quickly focus on an area of interest. The use of tables and figures provides clear examples and support to the text.

The only real weakness to the Guideline is its lack of authority since it is intended only as supplementary to existing Agency guidelines. Therefore whatever information is provided in the Guideline, it is all superseded by Agency-specific guidelines, protocols, and policies. Despite this limitation, the Guideline should prove useful to risk assessors both within governmental agencies and the external public,

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

Chapter 1 does a good job in introducing the elements and considerations involved in a microbial risk assessment (MRA) and some principles specific to microbial (versus chemical) risk assessments. The introduction briefly mentions a variety of different MRA guidelines and the common elements between them. The listing of these different MRAs in the reference section provides the reader with a useful list of references for future consideration. It is suggested that the electronic version contain more "hot links" between the references and their web addresses. Most, but not all government publications already contain these links, but most of the peer reviewed publications do not.

The glossary and abbreviation sections were useful, succinct, and complete. Again, as an aid to the reader, it would be useful to have a hot link to the EPA Thesaurus of Term for each entry.

The appendices are adequate and a helpful guide, but far from complete. Nevertheless, they provide a useful starting point for defining assumptions and outlining questions. Appendix A could be expanded with examples of specific assumptions identified from a variety of published MRAs. Hot links to these documents would provide a useful context for understanding how these assumptions were handled in the MRA.

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

The generic handling of microbial risk will be useful to risk assessors in a variety of scenarios, circumstances and regulatory contexts. The document is not so prescriptive or narrow as to limit its scope in any way.

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

Page 4, line 13-14. It is unlikely that the Guideline examines all relevant factors that impact risk assessments; particularly for specific applications. It is suggested that this sentence be revised to indicate that the Guideline attempts to examine the major (or principle) factors that impact microbial risk assessments.

Page 6, lines 5-15. The occurrence of stresses in environmental media (such as food or water) can impact the virulence of some pathogens. Environmental stresses may be reversed within the host, in which the case the pathogens may act like their unstressed counter parts. Alternatively stresses can have a profound impact on virulence. The risk assessor should be aware of these impacts and incorporate these considerations within the MRA. It would be useful to introduce the terms “stress” and “viable but not culturable” (VBNC) here.

Page 7, line 43. Inclusion of environmental stresses is also relevant here.

2. Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

The comments on Chapter 1 were provided in the response to question 1B above.

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

There was no superfluous information in the chapter. In fact, it would be good to emphasize the benefits of the iterative approach in the subsequent chapters (esp. 6 and 7).

3. Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

This reviewer found the chapter to be well written and comprehensive (perhaps the strong point of the Guideline). It answers the what, when, where, why, and how of planning and scoping. The numerous lists and questions provide a useful guide and examples of the planning and scoping process.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

Yes, I think it well addresses the needs of the stakeholders (e.g., risk assessor, risk manager/decision-maker, and interested parties).

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

Page 16, line 2. Provide text for abbreviation CFSAN.

Page 32, line 18. Agreed that MRAs can help evaluate the importance of data gaps and even rank their importance. But this cannot be done at the Planning and Scoping stage (*a priori*), so the context of this sentence needs some revision.

4. Chapter 3 – Hazard Identification and Hazard Characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

It is appropriate to define a hazard as both the nature of the pathogen itself and also the potential to cause an adverse effect due to a process breakdown, post treatment contamination, or lack of treatment. Overall the chapter does a good job describing the fist – the nature of the pathogen, but gives short consideration to consideration to process control. This has been a major challenge for EPA in drinking water regulations. For example, MRAs have done a good job in characterizing the nature of pathogens like *Cryptosporidium*, but struggle with characterizing the risk due to cross connection control where the risks come from a whole range of hazards. Moreover, with climate change there is a growing awareness of environmental change that is creating increased risks due to microbial agents. The focus of this chapter primarily on the characteristics of the microbe misses some of these larger hazard characterizations.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

Agreed that combining hazard identification and characterization is useful and logical.

Page 49, line 2. Suggest breaking this sentence into two to deal with the concept of “indeterminate types.” The major microbial categories that cause adverse outcomes are bacteria, fungi, viruses, protozoan, and algae. There is an additional category for indeterminate agents where the vehicle or pathway is important but the specific microbial agent can be indeterminate.

Section 3.8. page 53. It is important to consider how the analytical methods used for the hazard identification relate to the methods to characterize the dose-response. For example, molecular methods to identify and characterize the microbe in the food or water sample may have an entirely different level of

sensitivity than the cultural methods use to determine the dose-response curve. It would be useful to discuss how various techniques could impact the linkages between the various steps of the MRA process.

Page 53.line 40.VBNC should be defined as not “easily” grown on traditional cultural media rather than not culturable at all.

Page 54, lines 1-7. The role of disinfectants and processing (e.g., heat) in water and food are major stressors on microbes. It would be worth mentioning that consideration of stressed organisms is important for these applications.

Section 3.11. page 59-60. The consideration of environmental factors that impact microbial risk is very short. There are good examples of how habitat change and/or climate change have impacted microbial risks (e.g., Lyme Disease, cholera, hantavirus, etc.). Consideration of these environmental factors may be more important than detailed studies of the microbial occurrence.

5. Chapter 4 – Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

The chapter is well prepared and provides a good overview of microbial does response assessments. In particular, Table 4.1 provides a valuable summary of available dose response models.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

None.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

There are certainly animal and in-vitro does response models that could be used – particularly with appropriate safety factors – just as is done for chemical hazards. Such models could be used for pathogens that are too virulent or dangerous for human studies. There is nothing stopping EPA from adopting this course other than the pathogens examined to date have been relatively mild. The question is whether the Guideline needs to consider this question. This reviewer thinks the issue could be open with a brief discussion, but obviously this could entail the development of policies and procedures not yet available.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

This reviewer suggests careful review of the discussion of uncertainty and variability. As outlined in the glossary section, uncertainty related to the lack of knowledge and variability is related to the

heterogeneity in a parameter. Frequently the text refers to uncertainty as a factor in the variability of a risk assessment. The discussion of precision and variability should be carefully separated from uncertainty. Uncertainty doesn't necessarily result in increased variability (or a lower mean; page 82, line 31), it certainly adds to the lack of confidence in an assessment and risk management plans.

Page 63, line 45. It is *impossible* to empirically distinguish between very low non-zero and a true infectious threshold or just difficult? This sentence seems to contradict the section above (lines 37-44) which indicates that this is still an area of controversy. The following section (page 64) suggests that there is room for alternative theories – and it is good to outline the arguments.

Page 67, line 44. Watch terminology. Infection is not the same as colonization. Revise this sentence.

Page 68, line 2. Insert "multiplication and"… shedding of the pathogen….

Page 68, line 34. Suggest using the term "therapy" rather than treatment. This avoids confusion with treatment processes for food and water.

Page 70, line 8. Problems with the accuracy and completeness of annual surveillance statistics typically limit their usefulness for evaluating or validating MRA models.

Section 4.2.4. See the discussion of uncertainty and variability above.

Section 4.2.7. The use of uncertainty, modifying, or adjustment factors is primarily a policy issue. The practicality or science of these factors isn't as much as an issue as there hasn't been any policy to utilize these factors.

6. Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

This chapter on exposure assessment provides a broad overview of the issues involved in exposure assessment, but the unique aspects, particularly related to water systems – that related to the difficulties in evaluating temporal and spatial exposures are not well addressed. Additional discussion of treatment issues could be added to page 102, process modeling on page 107, and process data on page 119.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

Hydraulic models are increasingly being used to model the transport, exposure, and temporal and spatial variability of microbes in drinking water. Similar transport models for groundwater, rivers, and wind and currents in lakes have been used to examine exposures in these media.

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

See the discussion in 5D. For example, on page 94, line 8. Use can use probability distributions to characterize "variability" in exposures, but you can't use these for uncertainty (e.g., lack of knowledge). It is suggested that a word search be conducted to review the use of uncertainty and variability through the document.

Page 93, line 35. Suggest using "frequency" instead of "rates".

Page 103, line 28. It is suggested that the explanation of exposure routes be placed into a footnote in Table 5.2.

Page 110, line 24. Unclear why the consideration is for three "average" concentrations, rather the individual estimates.

Page 114, line 29 and page 120, line 34. Uncertainty or variability?

7. Chapter 6 – Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Because this section is a summary of guidance provided elsewhere it is an adequate summary of risk characterization, albeit it is an overview. Missing in this section is discussion of the iterative nature of the risk assessment process and how an important part of the risk characterization is the assessment of the data and a reiteration of the process. Too often the biggest criticism of the regulatory risk assessment process is that is it too linear to drive to a decision and reluctant to refine procedures to improve the decision-making process.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

Risk characterization is performed against specific goals. Although these goals are policy decisions, it would be useful to reference the various microbial risk goals used for various risk characterizations.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

This chapter is very short, and no, it does not provide details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping. Instead it relies on risk characterization guidance has been provided in greater

detail elsewhere. This is not necessarily a criticism of the chapter, but if the objective was to integrate the analysis of Chapters 3 – 5, this goal was not achieved.

Page 135, line 11. This section could consider the application of safety factors – particularly when uncertainty in the analysis is high.

Page 136, line 10. Scientific judgments can be strongly influenced by policy decisions and default or simplifying assumptions. For example, page 154 describes the impact of a 100-fold safety factor on chemical risk assessments.

8. Chapter 7 – Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

The chapter seems to have two messages; how a risk a mangers performs their job (down to managing budgets - see page 151, line 33), and how to complete a risk analysis to provide options for managing risks (see page 148, line 13). The later is far more important as a good risk model can be used to evaluate various risk management options. The chapter would be well advised to focus on this objective.

9. Chapter 8 – Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

The chapter does an adequate job in discussing risk communication and the role of the risk assessor in the process. There could be a better linkage to the planning and scoping chapter. For example, section 8.3 could emphasize the identification and communication with stakeholders should start with the planning scoping process. Likewise, section 8.14 could emphasize that risk communication is an iterative process that doesn't end.

10. Overarching Issues

10A. Overall utility of the Guideline

Overall, the Guideline provides a useful document to help guide a complicated process. Its publication should be a starting point for risk assessors and a useful overview for those interested in the risk assessment process (students, water professionals, etc.). Table 4.1 is a particularly useful summary of available dose response models.

10B. The flow and continuity of the document,

Besides the comments above where better linkages and be made within the chapters, over all the Guideline has a good flow and continuity.

10C. The consistency of the document, both in language and level of detail, across the chapters.

The Guideline is good with respect to language and level of detail, across the chapters. The question and answer format makes the Guideline easy to read. The reading level of the language and the ample references make the document useful for a wide range of audiences.

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors).

Yes, as mentioned above.

COMMENTS SUBMITTED BY

Patricia L. Meinhardt, MD, M.P.H.

Peer Review Meeting of EPA's Draft Microbial Risk Assessment Guideline:
Pathogenic Microorganisms with Focus on Food and Water

Comments submitted by Dr. Patricia L. Meinhardt

1. Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

I support of the Question and Answer format proposed by Interagency Microbiological Risk Assessment Guideline Workgroup in this draft MRA Guideline. The targeted audience has multi-factorial needs and responsibilities arising from varied statutory requirements and diverse Federal mandates. In addition, the complexity of characterizing and communicating the risks associated with waterborne and foodborne infectious diseases adds to the challenges facing the users of this MRA Guideline. In light of the fact that the intended audience for this Guideline is quite diverse and spans several professional disciplines, the approach incorporated in this MRA guidance document is appropriate for many reasons.

The MRA Guideline was developed to support and provide guidance to professional microbiologists and risk assessors conducting risk assessments of pathogenic microorganisms in food and water. In my opinion, the Question and Answer format is a very effective teaching tool that provides access to many fundamental concepts in an organized and structured fashion for a diverse group of end users. The Question and Answer format utilized in the MRA Guideline allows the user to quickly "drill down" to specific information of interest to them by viewing the *Table of Content* questions. Depending upon the infectious disease scenario facing the user, some portions of the Guideline will be more useful than others at any one moment in time. The Question and Answer format facilities ease of use and time efficient access to valuable information and guidance by many different professionals responsible for risk assessment, risk management, and risk communication during the course of an infectious disease event.

The Question and Answer approach proposed as the educational format in the MRA Guideline has precedence in other public health and medical venues. For example, the American Medical Association has a longstanding continuing medical education (CME) credit system for physicians to receive ongoing medical training and education throughout their careers. Several CME training modules and practice guidelines utilize a case report scenario followed by questions and answers as a successful format for educating healthcare practitioners and updating their skill set when new practice guidelines are released.

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful?

My comments regarding Chapter 1 are included in my response to Charge Question 2 below. The glossary, abbreviations, and references sections of the MRA Guideline are well done and provide appropriate support for use of the document. Appendix A and Appendix B are both worthwhile adjuncts to the content in the body of the Guideline and should remain in the Guideline as background materials, in my opinion. The example assumptions in Appendix A provide a good starting point for any risk assessor faced with assessing risk from an infectious disease event and provide a valuable outline of assumptions

to consider including general overarching assumptions as well as assumptions specific to the agent, host, environment, and exposure scenario under investigation.

Appendix B also provides important hazard identification questions for users to consider. However, I am concerned that several questions are very technical from a clinical perspective and may require some level of interpretation or consultation with a medical or public health specialist. Depending upon who asks the questions and in what setting this information is retrieved, some of the *Questions concerning the Host* (page B-3, lines 7-46) may border on confidential medical information and the resulting answers may need to be protected. This would be particularly important if the affected population under investigation was small in size and the retrieved information could be linked back to the affected individuals. For example, in a cancer cluster investigation with a population size of three or less affected individuals, special protective measures by public health specialists and risk communicators are required due to the possibility of unintentionally linking confidential medical information back to specific patients. Therefore, I would recommend adding the following qualifier to the introduction of Appendix B (page B-1, lines 1-5) which I have presented below in red font [underlined]:

Appendix B Hazard Identification Questions
This appendix contains examples of specific hazard identification questions that may be useful for the risk assessor's consideration. These are not all the questions risk assessors might consider. In addition, due to the nature of some of the questions, information gathering may need to be completed in collaboration with a public health or medical practitioner.

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

I understand that the intent of this MRA Guideline is to provide guidance on microbial risk assessment with an emphasis on pathogenic organisms in food and water but that the document has been prepared to have application to other scenarios, circumstances, and regulatory context. I agree that this MRA Guideline has the potential for broad application and generalizability in other settings and provides an important model for other pathogenic microorganisms of concern such as weaponized biological agents and emerging microbial agents. Since the Guideline is intended to be a living or "evergreen" document, it has the capacity to be modified as more information becomes available. As the work group has indicated, appropriate modules for new guidance can be added and revised in the MRA Guidelines as new challenges arise. The Question and Answer format used in the Guideline lends itself to modification with new information and updating of current information. Therefore, I support the viewpoint that the approach utilized in the existing MRA document would be suitable for planning, assessing, and analyzing risk resulting from exposure to other types of microorganisms of public health concern not addressed in the current draft.

2. Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

Chapter 1 successfully outlines the need for the MRA Guideline as well as provides a historic context for the development of this guidance document. The *Introduction* effectively defines: 1) the need for and the benefits of the MRA Guideline; 2) the applications for use of the Guideline; 3) the relationship of the new Guideline to other MRA guidance; 4) the major principles of an effective MRA; 5) the fundamental differences between microbial and chemical risk assessment; and, 6) the disease triad of infectious disease that is a critical concept for a MRA. In my opinion, this introduction is well written providing a proper introduction and convincing argument for use of the guidance by risk assessors and other professionals.

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

This MRA Guideline is a comprehensive and complex document that requires a robust introduction in length and an emphasis on key risk assessment concepts. I do not believe that the chapter needs to be shortened as the information presented is vital to understanding the importance of this guidance document. However, I would suggest that the order of two sections of the *Introduction* be changed to provide improved flow of the information presented. I would recommend that the work group consider moving the following sections to the end of the chapter rather than presenting this information in the middle of the chapter: 1) Section 1.5: What are Some Fundamental Differences between Microbes and Chemicals? (Page 5, line 40 through page 8, line 35) and 2) Section 1.6: What is the Relationship of Infectious Disease to Human Health as Applied in a MRA (page 8, line 37 through page 9, line 4).

3. Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

I cannot comment on the more technical aspects of this chapter, but from my perspective as an occupational and environmental medicine physician, I believe that the work group has summarized and clearly articulated the essential components and concepts regarding planning and scoping as set forth in established practices by other authoritative sources. The chapter provides an excellent discussion of important considerations for problem formulation and other aspects of planning and scoping of a MRA including: 1) definitions, benefits, and decision criteria; 2) description of interested parties and stakeholders; 3) applications of a MRA with examples; 4) listing of example products of planning and scoping; 5) critical assessment of information/data quality; and, 6) responsibilities of a risk assessor.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

The work group has effectively addressed the needs of both internal and external stakeholders during the planning and scoping phase of a MRA in this chapter, in my opinion. The chapter emphasizes a multi-disciplinary approach and the need for the involvement of disparate parties in the planning and scoping

phase of a MRA to improve the outcome of the assessment. This is often not an easy task for a risk assessor faced with pressures from many stakeholders, often with contradictory interests. Section 2.4 (page 19, lines 8-45 through page 20, lines 1-25) provides a sensitive discussion of which stakeholders may be involved in a MRA and the complexity of how and when their input would be appropriate in the planning and scoping process.

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

I find this chapter well-written and a useful summary of the essential components of scoping and planning necessary for initiating and conducting a MRA.

4. Chapter 3 – Hazard Identification and Hazard Characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

From a clinical perspective, I support the framing of a microbial hazard from both the nature of the pathogen and also the potential to cause an adverse health effect. Addressing the qualitative elements of a hazard (identification and characterization) is a valid first step followed by the quantitative assessment of a hazard (dose response assessment), in my opinion. I believe that this chapter successfully describes the importance of hazard identification and characterization as essential components in MRA and effectively orients a risk assessor to the appropriate methodologic approaches for defining pathogenic infectious disease hazards.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

I support the authors' approach of combining hazard identification and hazard characterization as presented in Chapter 3 of this MRA document. I believe that this new risk assessment paradigm is quite logical and does allow for an improved portrayal of a hazard resulting from a waterborne or foodborne pathogen exposure. Combining the qualitative elements of a hazard (identification and characterization) followed by the quantitative assessment of a hazard (dose-response assessment) has validity from my perspective.

When evaluating a foodborne or waterborne infection in a patient, the diagnostic and treatment process requires combination of hazard identification and characterization in order to address both the pathogen under diagnostic consideration and the treatment protocol necessary to effectively manage the adverse health effect of the pathogen. As a treating physician, combining hazard identification and hazard characterization is often the most appropriate approach to addressing the negative sequelae associated with the infectious pathogen and the potential impact on the health of the patient. In light of this clinical practice, I find that combining hazard identification and characterization is a much more logical means of addressing human health risk from waterborne and foodborne pathogen exposure. That said, defining the infective dose of an infectious pathogen is essential information during the diagnosis and management of

a patient as it is in any MRA during dose-response assessment. Nonetheless, combining qualitative aspects of hazard identification and characterization has significant legitimacy and improved utility in MRA, in my opinion. Addressing the importance of dose-response assessment and associated modeling approaches is best presented in a separate chapter as proposed by the workgroup.

5. Chapter 4 – Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

From a general perspective, I believe that the microbial dose-response assessment chapter in the MRA Guideline provides appropriate, useful, and understandable content in a detailed and clearly articulated fashion. The chapter organization with two sections separating general considerations (Section 4.1) from current practices (Section 4.2) is a well-designed and worthwhile approach. I found Section 4.1.3 (pages 63-70) and Section 4.1.4 (pages 70-71) particularly informative for many users.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

As an occupational and environmental medicine physician, addressing this question is outside of my area of expertise and I offer no response.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

As an occupational and environmental medicine physician, addressing this question is outside of my area of expertise and I offer no response.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

The uncertainty and variability in dose-response findings is clearly described in this chapter in Section 4.2.4, Section 4.2.5, Section 4.2.6, and Section 4.2.7 (pages 82-85). These sections describe the inherent uncertainty and inescapable variability in the interaction between a host and pathogen and the resultant impact on dose-response findings. The work group included some useful strategies for evaluating uncertainty and accounting for life stages and sensitive subpopulations as well as a discussion of the appropriateness of using modifying and adjustment factors.

6. Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

From my perspective as an occupational and environment medicine specialist, this exposure assessment chapter provides appropriate, useful, and understandable content for a varied audience of risk assessors, risk managers, decision-makers, risk communicators, stakeholders and the general public, and researchers. This chapter of the MRA Guideline is the most likely to have utility for a diverse audience of multi-disciplinary professionals and external stakeholders with varying degrees of technical proficiency. I believe that the chapter is very robust and provides detailed explanations of complex concepts that are essential to understanding exposure assessment. I found the material in Section 5.2.1 – 5.2.4 (pages 99-106) particularly informative.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

As an occupational and environmental medicine physician, addressing this question is outside of my area of expertise and I offer no response.

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

The uncertainty and variability inherent in exposure assessment is clearly described in this chapter in Section 5.1.7 and Section 5.1.8 (pages 92-93) as well as throughout other sections of the chapter. In my opinion, the concept of uncertainty that requires formulating difficult exposure assessment decisions with serious public health consequences in the face of imperfect data has been successfully delivered by the work group in this important chapter.

I note the following public comment submission offered by George Arvanitakis from Health Canada referring to Section 5.4 (page 127) of this chapter:

Pg.127, section 5.4: would it be possible to assign a qualitative description (low, medium, high) to the overall likelihood of exposure at the end of a microbial risk assessment? If yes, how? Would this be useful in risk communications to the public?

This comment proposes an interesting model that the working group may want to consider adding to this exposure assessment chapter. When I evaluate human health risk from chemical contaminants in water, I often “tier” the quantitative exposure data into low, medium, and high qualitative categories for both risk communication and resource allocation for medical monitoring. This translation from quantitative to qualitative categorization is not always feasible but it may be worth presenting as another risk communication tool in this MRA Guideline.

7. Chapter 6 – Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

I agree with the working group's decision to refer the Guideline users to other references that address risk characterization in great detail such as the National Research Council reports, the EPA's *Risk Characterization Handbook*, and *An Examination of EPA Risk Assessment Principles and Practices*. In my opinion, this chapter successfully summarizes the guidance necessary to: 1) provide a microbial risk assessor with what information to include and how to integrate the information from Chapter 3-5 in an appropriate risk characterization and 2) address the questions posed during the planning and scoping process addressed in Chapter 2.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

I am unaware of any additional risk characterization guidance references that would be appropriate to add to this MRA Guideline.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

Refer to my comments in 7.A above.

8. Chapter 7 – Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

This chapter provides useful information for microbial risk assessors regarding why they are conducting a risk assessment and what they need to be aware of when interfacing with risk managers and decision makers. Since it is not intended to be a fully detailed guidance on risk management itself, I believe that the authors have summarized the most important concepts of risk management and have defined many confusing terms in an effective manner. The content of this chapter should provide the appropriate background needed for risk assessor to communicate and collaborate with risk mangers and internal and external policy and decision makers.

9. Chapter 8 – Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

In my opinion, this chapter is exceptionally well done and acts as a valuable primer for risk assessors regarding how their risk assessment analyses and conclusions can be effectively communicated to various stakeholders interested in their risk assessment. The authors have achieved the goal of providing basic information on the risk communication responsibilities of the risk assessor and providing direction for collaboration with others responsible for risk communication itself.

10. Overarching Issues

10A. Overall utility of the Guideline,

10B. The flow and continuity of the document,

10C. The consistency of the document, both in language and level of detail, across the chapters,

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors).

In my opinion, this MRA Guideline reflects a thorough and thoughtful review of the existing scientific literature and captures "best practices" in risk assessment, risk management, and risk communication. This Guideline is a valuable "road map" for microbial risk assessment and is a significant contribution to the risk assessment literature in general. The Guideline has the potential for broad application and generalizability in other settings for a diverse audience of stakeholders and users. The guidance document also provides an important model for assessing other microorganisms of concern beyond foodborne and waterborne pathogens. The Question and Answer format allows the Guideline to be a living or "evergreen" document with the capacity to be modified as more information becomes available. As the work group has indicated, appropriate modules for new guidance can be added and revised as new challenges arise in the future adding to the utility of this working document well beyond the current version.

The flow and continuity of this document as well as the consistency in the level of detail and content complexity are impressive. This guideline has successfully incorporated an overarching approach to conducting microbial risk assessment that can be used as a template with the capacity for flexibility as needed. This template approach promotes consistency and improves transparency in how microbial risk assessments are conducted and introduces risk assessor users to "field tested" tools and strategies.

The subject of risk assessment, risk management, and risk communication for foodborne and waterborne pathogens is complex and often contentious. I believe that this draft MRA Guideline has struck a balance in both the detail and summary of complex information to provide a readable and user friendly guidance document for microbial risk assessors and others. The Interagency Microbiological Risk Assessment Guideline Workgroup should be commended for their efforts in developing this valuable MRA guidance document.

COMMENTS SUBMITTED BY

Christine L. Moe, Ph.D.

Peer Review Meeting of EPA's Draft Microbial Risk Assessment Guideline:
Pathogenic Microorganisms with Focus on Food and Water

Comments submitted by Dr. Christine L. Moe

1. Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

The overall format of the Guideline is fair. It is not the best organized didactic tool I have ever seen, and there is some redundancy. However, the overall outline of the document is logical. The use of questions as section headings in each chapter is helpful for indicating the content of each section. Some of the subheading titles are not informative, for example: "Culture related issues" (pg 53, line 29) or "Process Data" (pg 119, line 24).

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

The list of abbreviations is critical – especially for someone new to this field.

The glossary is helpful although I noticed some terms in the text that were not included: e.g., "allelic ratio" (pg 6), "ecological risk assessment" (pg 44 and earlier), "taxon" (pg 44), "stressor".

Appendix A: It is helpful to include this appendix. The reader should be cautioned that these are **Example Assumptions** (as the title states) but that some of these assumptions may really not be appropriate in some situations. Page A-1 "MRA's" on lines 23, 27 and 45 should be "MRAs" i.e., without an apostrophe. On these lines, the term is plural, not a contraction or possessive form of a noun.

Appendix B: Overall, this seems like a reasonable set of example questions. It is useful to include this appendix. The questions should be screened again. Some specific questions do not seem useful - e.g., Question #9 on page B-2 and Question #38 on page B-5. Also, there is some redundancy in these questions – e.g., Question #34 on page B-2 and Question #22 on page B-4 appear to be the same. There are several other questions that also seem very similar to each other.

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

The best way to make this Guideline more useful is to provide a wide range of examples that illustrate different types of microbial risk assessments for different purposes.

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

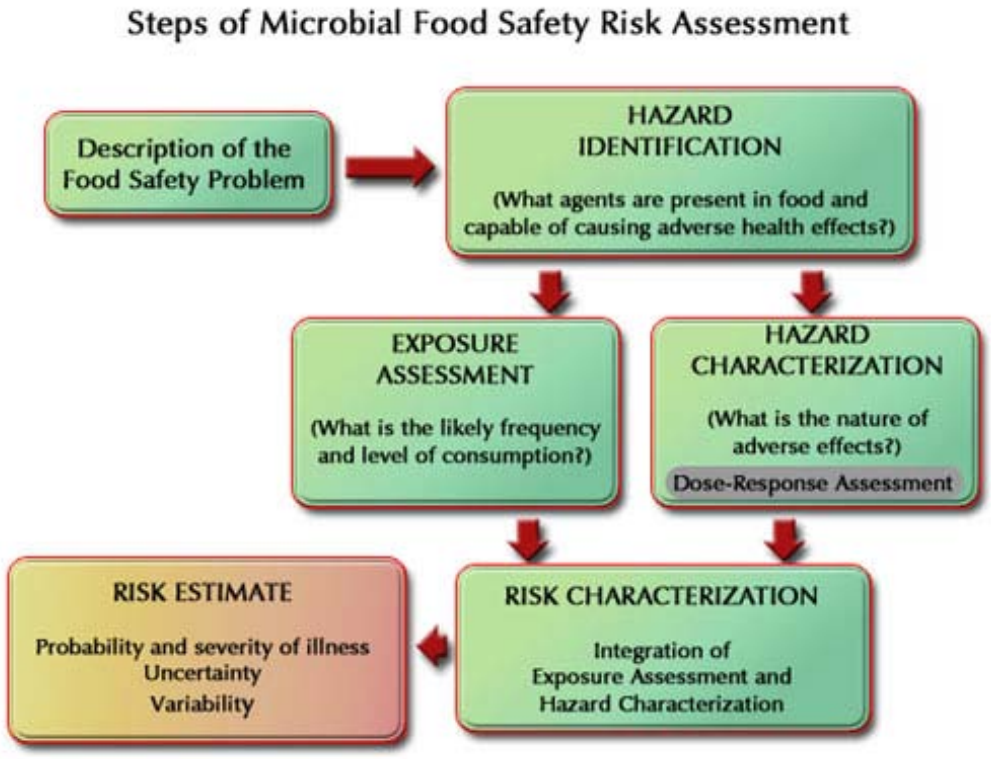
The best way to make this Guideline more broadly applicable is to provide a wide range of examples that illustrate different types of microbial risk assessments for different purposes.

It would be helpful to explain how the microbial risk assessment approach described in this Guideline is (or is not) compatible with international guidelines for microbial risk assessment beyond the USA (e.g., WHO MRA approaches).

2. Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

This chapter would really benefit from the addition of better diagrams. Figure 1.1 and 1.2 are ok, but there needs to be a diagram that really illustrates the whole risk assessment process. Maybe something like this:



From: http://smas.chemeng.ntua.gr/MIRAM/

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

Section 1.6 on page 8. The title of this section does not make sense and does not accurately reflect the concept illustrated in Figure 1.2.

Section 1.10 from page 11 – 14 is just a "laundry list" of principles for MRA gleaned from other sources - ten "general principles" from one source, four "major principles" from another source and finally, six principles from a third source. This is too many "principles" and is quite repetitive. Finally, this chapter ends with the statement "These principles have been incorporated throughout this Guideline." This leaves the reader wondering if all 20 principles (10+6+4) are really incorporated throughout the document?? It would be better to really go through all these 20 principles and distill them down to a few major points.

A few comments on grammar:

Pg 1, line 13. "Layout" is not a verb.

Pg 1, line 43. "Federal" should not be capitalized.

Pg 2, line 23. "Agencies" should not be capitalized here and in many other sentences in this chapter when it is not used as a proper noun.

It is confusing how this chapter starts by referring to "the risk assessor" and then changes to address the reader directly as "you" (page 5).

3. Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

This chapter presents a large amount of information, and most of this information is presented at the same layer of organization. It would be helpful to the reader if this chapter was organized better. Many topics are presented for consideration, but the logical order of what should be done first and what are the next steps is not clear. It would be easier for the reader if this planning and scoping process is explained as a series of steps. It may be most logical to start with the WHY sections (2.3 and 2.5), before moving on to the WHO section (2.4) and the HOW sections (most of 2.6). Some sections, like 2.5.3, seem to be too much detail at this stage.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

Not my area of expertise.

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

The chapter should start with defining "planning and scoping" in the first sentence and then explain how this will help ensure relevance of the risk assessment.

All of the EPA and FDA guidance documents that are cited on the first page of this chapter (lines 6, 15, and 31) could be listed in a separate section at the end of this chapter called "Where to find more information". The same applies to the documents referred to on page 21, lines 15-21.

It would be helpful to the reader if there were some examples of key points – such as a problem formulation statement, a figure with a conceptual model diagram, a text box that outlines an analysis plan.

There are a lot of "lists" in this chapter. Do all of these belong in the body of the text or would some of these lists be more suitable in text boxes?

4. Chapter 3 – Hazard Identification and Hazard Characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

- This chapter needs some reorganization because it is hard to follow.
- There is too much emphasis on hazard identification and detail on microbial typing methods.
- There is too much technical information in this chapter that will be confusing for someone who is not a microbiologist. This level of technical information is probably not necessary for a risk assessor.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

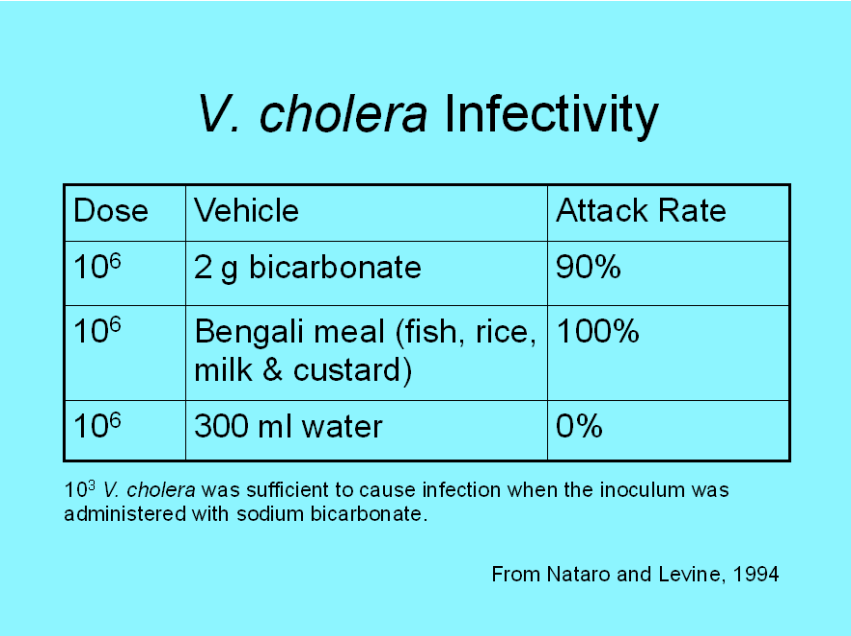
Need to clarify when discussing detection of microorganism in human clinical specimens vs. environmental samples

5. Chapter 4 – Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

Overall, this chapter is well written, and the material is presented at an appropriate level.

In the description of exposure medium (page 65-66), it would be helpful and interesting to add a text box showing the data from the *Vibrio cholera* human challenge studies that clearly illustrate differences in infection/illness of subjects who ingested the same *Vibrio cholera* dose in food vs. water vs. water after ingesting bicarbonate of soda. (I will find the reference for this study.)



V. cholera Infectivity

Dose	Vehicle	Attack Rate
10^6	2 g bicarbonate	90%
10^6	Bengali meal (fish, rice, milk & custard)	100%
10^6	300 ml water	0%

10^3 *V. cholera* was sufficient to cause infection when the inoculum was administered with sodium bicarbonate.

From Nataro and Levine, 1994

In the explanation of human challenge studies on page 68, it would be helpful to explain that clinical specimens (stool, vomitus, sera, saliva, PBMCs, etc.) are collected before challenge and for days to weeks post-challenge. These specimens are used to determine infection status, pre-challenge immune status and immune response to infection.

On page 68, lines 1-3, it is important to explain that seroconversion is the **change** in pathogen-specific antibody levels between pre-challenge sera and post-challenge sera. The presence of pathogen-specific antibody in pre-challenge sera indicates prior infection with the pathogen (but not necessarily the same strain as that in the challenge inoculum). Detection of pathogen-specific antibody in pre-challenge sera MAY or MAY NOT indicate protective immunity.

On page 68, lines 10-12, please provide the reference for the Salmonella dose-response relationship for illness.

Page 70, section 4.1.4: It would be helpful to introduce and explain the concept of the Basic Reproductive Number (R_0) as a measure of infectivity and modeling the spread of the disease in the population. R_0 is usually defined as "the expected (average) number of new infectious cases in a completely susceptible population produced by a single case during its entire period of infectiousness." (http://wiki.medpedia.com). There can be a large range in R0 – depending on the pathogen, setting and characteristics of the index case (such as whether the index case was a food handler or someone who had the opportunity to come into contact with many susceptible hosts).

Pages 71 and 77 – The discussion of host susceptibility should include a brief explanation of how immune response is measured. There is a difference between immune response to infection (e.g., production of pathogen-specific serum antibodies) and development of protective immunity. For some pathogens, serum antibodies do not appear to provide protection from subsequent infection. Pathogen-specific antibodies

can be considered a marker of previous infection and of host susceptibility to the pathogen. It should also be explained that for some infections, previous infection may increase the probability of illness in subsequent infections (e.g., Dengue, and maybe *Cryptosporidium*?).

Page 71, lines 32-35. Please explain what is meant by "non-intuitive results". It would be helpful to have a more explicit explanation of the pros and cons of including or not including secondary transmission in the risk assessment.

Although I am not a mathematician, I was able to understand most of the description of the various models and the differences between them. For each of the mathematical models presented in section 4.2.1, it would be really helpful to show an example data set from a human challenge study and a graph of the dose-response model. Further explanation is needed to describe how all the inputs into the models can be probability distributions – such as the dose, alpha and beta. But these distributions need to be based on actual data.

Editing note: Pgs 76-77 - Please refer to the equations in the text as "Equation 4.1" rather than "Equation 1" (same for all the equations in this chapter).

Page 80, lines 1-12 – Please explain the relationship between dose and incubation period. Usually, the larger the dose is, the shorter the incubation period between exposure and infection or symptoms. Also, under certain circumstances, it is possible to have morbidity at low dose than high dose if it is an organisms that causes a lot of tissue damage and the host immune response is slow.

Page 80, line 31 – How does this Guidance manual define "valid dose-response data set"?

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

I am satisfied with the information provided in Table 4.1 (pgs74-75). It would be helpful to indicate which of these dose-response models were fit to human challenge data and which use data from outbreaks. Also, please indicate if any of these models are based on animal data and which animal. Please modify this table to include information on which strains of each pathogen were included in each model. For example, there have been human challenge studies with multiple strains of *Cryptosporidium*.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

I agree with the perspective presented in this chapter – i.e., that in certain situations, animal or in vitro data may provide some useful information such as the range in virulence between different strains of Listeria in mice (pg 69, lines 28-29). I do not recommend trying to translate animal dose-response data to human dose-response data.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

There are additional sources of uncertainty and variability that should be included in this discussion:

- Most human challenge studies do not attempt to test very low doses of a pathogen because of sample size limitations. So the dose-response relationship at low doses (that may be most representative of contamination levels encountered in food and water) is extrapolated based on the type of model fit to the data in mid- to higher doses.
- There can be some variability in the titer of dose given to individual subjects in a challenge study – depending on how the dose is prepared and the sensitivity and reliability of the titering method. There can also be variability in titering the inoculum used in the challenge study.
- There can be uncertainty in characterizing host susceptibility. Some hosts may have unknown genetic factors that make them resistant to a particular pathogen even at high doses (e.g., Norwalk virus, see Lindesmith et al., 2003). This may introduce noise in the data used to model the dose-response relationship.
- There can be uncertainty in correctly classifying a challenged volunteer as "infected" or "ill". There are times when a challenged volunteer may exhibit symptoms but no signs of infection (detection of pathogen in stool or seroconversion). There can be a range in symptoms and definitions of "illness" may vary between studies. Symptoms can be a very unreliable measure of infection. This could explained better on page 67, lines 40-43.
- Most human challenge studies have small numbers of subjects. There may be few doses tested and small numbers of subjects at each dose. Uncertainty about the classification of the infection status or illness status of a single volunteer may have a large impact on the results at a single dose level and may affect the accuracy of the dose-response model.

Pg. 69 – The chapter correctly points out that human dose-response information can also be obtained from outbreak analyses and explains the advantages and limitations of this data. It is important to point out that outbreak investigations can also provide information on the frequency of a range of outcomes for the general population and sensitive sub-populations: infection (based on laboratory diagnosis), self-reported symptoms, medical visits, hospitalization, sequelae such as hemolytic uremic syndrome, mortality. This information can be valuable for risk assessment as well as economic analyses.

Pg. 84, lines 30-34 – it would be helpful to have a text box with a table or figure that shows the results from the Englehardt and Swartout 2004 risk assessment that includes assumptions about sensitive and resistant populations.

Pg 85, line 1 – please explain "receptor populations"

6. Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

The figures in this chapter, specifically Figure 5.4, 5.5 and Table 5.3 were extremely helpful in illustrating some key ideas in this chapter. The whole Guideline needs more examples with flowcharts and tables like these. The beginning of this chapter should include a step-by-step flow diagram of how to put together an exposure assessment.

Pg 87, line 14 – Many environmental exposures will be recurring events rather than single events. A contaminated water source may be contaminated for days. Fomites may have infectious agents on them for days before they are cleaned or the agent dies off. It may be necessary to account for repeated exposures in a microbial risk assessment.

Pg 90, lines 11-19 – please include exposure via hand-to-hand contact.

Pg 91, lines 1-4 – please give examples of ecological niche. “n-dimensional hyperspace” is not a very informative description.

Pg 91, line 18 – please replace “Things like” with “Conditions such as”

Pg 91, lines 37-42 – please explain that a qualitative exposure assessment may be needed if there is no acceptable method to translate human behavior or activities into quantitative terms.

Pg 96, line 10 – “What can go wrong?” is not a very useful perspective because it is so narrow. You may want to ask “What could change?”

Pg 96, line 37 – please explain “scenario triplets”

Pg 98, line 24 – it would be helpful to include an example scenario

Pg 100 line 24 – pg 101, line 2 – it would be helpful to show an example of an “explicit diagram” with “meaningful symbols”

Pg 102-103 – these three examples are very helpful. These could be put into a text box.

Pg 103, lines 22-33 – this seems like introductory material that should be at the beginning of this chapter.

Pg. 112, line 11 – please do not use “prevalence” when discussing microbiology data because this term has a specific epidemiology meeting. In this sentence, it makes more sense to use the term “frequency” or “proportion” instead of “prevalence”.

Pg. 113, Table 5.3 – It would be helpful if you define the variables in a footnote at the bottom of the table.

Pg. 115, line 3 – There is a typo where N_t and N_0 are shown as superscripts.

Pg. 115, lines 27-41 – This example of sources of variability seems rather narrow. You could also mention attenuation due to natural die-off in the environment as well as inactivation by water treatment processes. Data on human food handling behaviors can also be collected through structured observations or even video cameras.

Pg 116, lines 30-35 – It seems like this information is just thrown into the chapter but not related to the bigger picture.

Pg 116, lines 37-41. This paragraph is about transport of microbes in the environment. Transport examples in both indoor and outdoor environments should be discussed and the factors that affect transport. For example, there are number of factors that affect the movement of microorganisms in the soil and potentially into groundwater – such as rainfall, soil type, adsorption and desorption, surface charge of the microorganism, pH, etc.

Pg 117, lines 25-34 – This information seems like a repeat of information in Chapter 4, pg 71. Maybe this should be consolidated in one area of the guideline. Also, there should be an additional category of people who have asymptomatic infections.

Pg 118, lines 26-28. This statement is not very helpful or informative.

Pg. 118, lines 30-44 – The subtitle "Data on Microorganisms" is very vague and not informative. Please use the term "occurrence" when describing detection of microorganisms in environmental samples instead of "prevalence" because "prevalence" has a specific meaning for epidemiologists, i.e., number of cases of a specific disease or condition per population at a given time or age.

Pg 119, lines 1-2 – immunological assays are almost never used to detect microorganisms in environmental samples. There may be cross-reactivity in some molecular assays (such as PCR) if the primers or probes are designed to detect a group of organisms.

Pg 119, line 24 – not a very informative title for this section. Also, this section seems to repeat information that was provided earlier.

Pg 127 – Please **show examples** of Exposure Assessment Reports and graphical formats and tables for presenting risk results (lines 17-18), and examples of conceptual model diagrams (lines 29-31), and how to list inputs used in the model and graphical depictions of their distributions (lines 33-37).

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

This chapter provided little guidance on developing environmental sampling and analyses strategies to specifically inform data gaps in microbial risk assessments. For example, if you want to do an assessment of the risks from wastewater irrigation of produce (which is standard practice in many parts of the world), how could you design a sampling strategy to collect data on microbes in wastewater and microbes on the produce in order to develop a useful and relevant exposure assessment? How many samples would you need? How many types of produce should you investigate? What should be the minimum spatial consideration (number of farms? Number of regions?) and temporal consideration (daily samples? Weekly? Monthly?). How can MRA or QMRA inform these sampling decisions?

Please add discussion about biomarkers of exposure and how to interpret serum antibody or salivary antibody data.

Table 5.2 – in the first column, it would be helpful to add "Human or animal". In the third/fourth column, it would be helpful to add "vehicle" to the heading and add "sand" – maybe next to surface soil or sediment.

Pg 105, lines 18-20 – In addition to exposure routes, it can be helpful to think of exposure activities that may put someone at risk, such as fertilizing a garden with manure, cleaning out a cat litter box, visiting a petting zoo, foreign travel, living with a small child who attends daycare, etc. Most of this information is collected through questionnaires or interviews. Sometimes, information on risk activities or behavior is collected through structured observation studies.

Pg 105-106 – People who live in an institutional setting (with shared meals and shared bathrooms) could be considered a special subpopulation.

Pg. 106, line 26-29 – explain where there are data on number of human illnesses per year caused by specific microorganisms – such as diseases covered by surveillance systems, reportable diseases, etc.

Pg. 107, Figure 5.2 – This figure is helpful but it would be more helpful if it illustrated a specific example of a specific microbe and used data on different sources.

Pg 109, section 5.2.5 – this section may belong on pg 96 with section 5.1.12

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

Pg. 125 – In the discussion about sensitivity and uncertainty analyses, it would be helpful to point out that these analyses can help identify critical data gaps and help prioritize research needs.

Pg 128, lines 8-12 – Please show examples of the "results of sensitivity and uncertainty analyses in tabular or graphical formats".

7. Chapter 6 – Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Pg 132, lines 37-43 – The explanation of risk description in this paragraph is helpful.

Pgs 132-135 – many of the elements of risk characterization were also in the planning and scoping phase. The risk characterization is similar to the "Discussion" section of a scientific paper and should close the loop on the issues that were raised in the planning and scoping phase.

Pg 141, Figure 6.2 – This figure is appropriate for an organism like hepatitis A virus where someone has lifetime protective immunity after infection. However, this diagram is not accurate for organisms like norovirus where there can be repeated infections after exposure to the same strain. Infection may solicit an antibody response but this may not be a protective immune response.

Pg 141, line 11 – is the "miss-estimation" and underestimate or overestimate?

Pg. 142, line 1 – give some guidance on how "small" a population is the stochastic form appropriate for.

Pg. 142 – some of the information here is a repetition of information on pgs 124-125. Try to consolidate this discussion of sensitivity and uncertainty.

Pg 144, Table 6.1 and lines 9-16 – please provide some guidance on **when** it is appropriate to use each of the approaches listed in the table and text below.

Pg 145 - explain how DALYs and QALYs are derived and discuss the strengths and weaknesses of these metrics and when it is appropriate to use them.

Pg 145, lines 30-41 – Agree that it is important to include economists as part of the risk assessment team, but this does not really fit in a section on "How are Quality of Life Measures Important in MRA?". There is a typo on line 34.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

8. Chapter 7 – Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Pgs. 149-150, lines 19-26 and 1-10 – It is not useful to list these 8 principles from another document and not provide any commentary.

Pgs 153-154, lines 23-44 and 1-17 – again, this is a list of different approaches. There is some discussion about the pros and cons of each approach, but there should be a summary commentary at the end that provides guidance on which of these approaches are most relevant for microbial risk assessment

9. Chapter 8 – Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

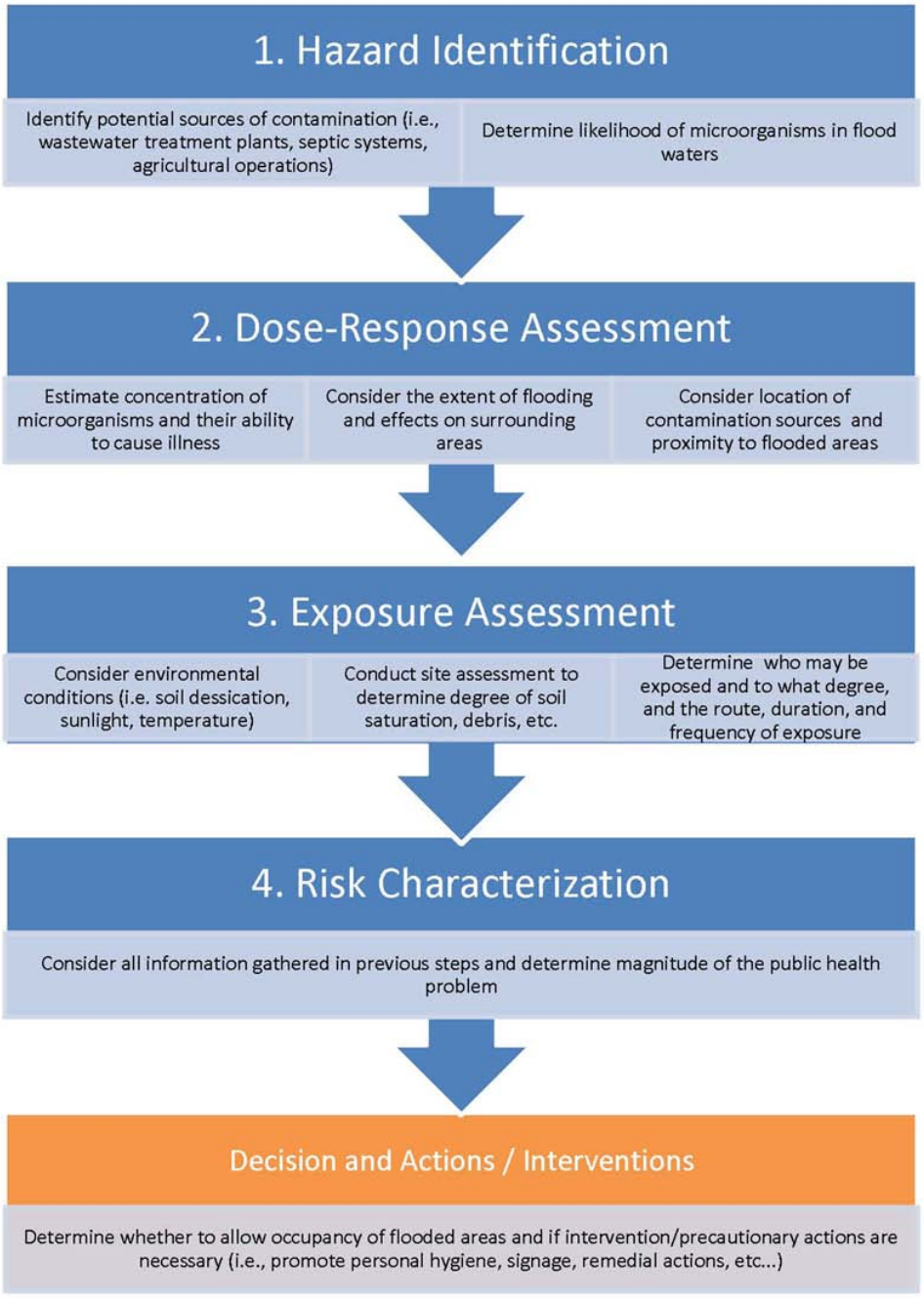
No comments.

10. Overarching Issues

10A. Overall utility of the Guideline

The MAJOR weakness of this guideline is that it provides too few examples, figures and flow diagrams to illustrate the concepts that it is trying to communicate. For most of these concepts, a picture would truly be worth a thousand words in getting across the main ideas to the reader. Also, text boxes with examples of microbial risk assessments for food safety, water safety and other situations with environmental microbial hazards would make the concepts more clear and make the document **much** more interesting to the reader as well as a better didactic tool. An example of a very basic flowchart illustrating risk assessment (for a flooding situation) could be something like this from the CDC website. Something like the figure below, that has been modified to illustrate microbial risk assessment, could fit into Chapter 1 and/or Chapter 6.

Figure 1. The Four Steps of the Risk-assessment Process



From: http://www.cdc.gov/nceh/ehs/Publications/Guidance_Flooding.htm

I am surprised that I don't see any discussion about on-line tools and resources for microbial risk assessment mentioned in this Guideline. It would be helpful to add an appendix about on-line tools and resources (databases and software packages) for modeling and risk assessment – such as "Crystal Ball", "@Risk", and "Berkeley Madonna". WHO has global health databases that may be useful for risk assessment (http://apps.who.int/ghodata/). The JIFSAN Institute (http://jifsan.umd.edu/), funded by FDA

at the University of Maryland, also has databases for risk assessments. The Center for Advancing Microbial Risk Assessment at Michigan State University website states that it is developing QMRA tools as standalone computer applications, but I do not see these available on their website.

10B. The flow and continuity of the document,

This was not an easy document to get through even when spread out over several days. The introductory paragraphs at the beginning of each chapter are helpful to give an overview of the topic of the chapter. The document would be stronger if there was also a summary section at the end of each chapter – either one or two paragraphs or a bulleted list of key points that are the "take home messages" of the chapter. I also recommend moving some of the references in the text for additional information to the end of each chapter as a section on "Where to go for more information" on specific key issues that are covered in the chapter.

10C. The consistency of the document, both in language and level of detail, across the chapters,

The writing quality is uneven in the document. Chapters 4 and 5 are well written. Much of Chapter 3 was difficult to read even though I am a microbiologist. The level of detail in this chapter is too much for a risk assessor - please see my specific comments on this chapter above. Chapters 1 and 2 need editing by a professional editor. There is incorrect use of uppercase letters, incorrect use or absence of commas, and the writing voice changes from referring to "the risk assessor" to "you".

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors).

This document has way too much detail to be useful to most stakeholders. A shorter document that is entitled something like "Introduction to Microbial Risk Assessment and Its Use in Decision Making" would be better suited for stakeholders. **If** this document adds some good flow charts and conceptual diagrams, these may be applicable for communicating with stakeholders.

REFERENCES CITED IN THESE COMMENTS:

Lindesmith, L, **CL Moe**, S Marionneau, N Ruvoen, X Jiang, J Lindblad, P Stewart, J LePendu and R Baric. (2003) Human susceptibility and resistance to Norwalk virus infection. *Nature Med* 9(5):548-553.

COMMENTS SUBMITTED BY

Gary S. Sayler, Ph.D.

Peer Review Meeting of EPA's Draft Microbial Risk Assessment Guideline:
Pathogenic Microorganisms with Focus on Food and Water

Comments submitted by Dr. Gary S. Sayler

1. Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

Following the introduction of Chapter 1, Chapters 2-5 are organized around the topics of planning and scoping, hazard identification and characterization, dose response assessment, and exposure assessment, respectively. This is a logical progression of chapter organization as these topics are principle elements of the MRA (microbial risk assessment). There is some uncertainty why hazard identification and characterization are combined in one chapter (chapter 3); when, in the introduction (page 5) they are listed as individual elements suggesting they have equal weight individually as that given to the scoping, dose response, and exposure elements of MRA. Chapters 6-8, cover risk characterization, risk management, and risk communication as essential outputs from the MRA process. This appears to be an appropriate placement of these topics as they are written to inform the risk assessor of the delivery of the MRA results with transparency, clarity, and utility. Chapters 2-5 are information rich but, to an extent, are delivered with a degree of unevenness with respect to technical detail, explanation and perceived expertise of the risk assessor. On the other hand; Chapters 6-8 offer more uniformity in the level at which information is delivered to the reader.

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

Chapter 1, (introduction) is clearly needed as it provides both extensive amount of background material on the MRA itself an explanation as to why the Guideline is needed as a broad framing document for microorganisms with potential utility to other risk assessment paradigms. The collaborative effort to harmonize the Guideline for Pathogenic Microorganism of concern by multiple agencies for two distinct environmental sources, food and water, is greatly appreciated and well developed by the introduction.

As expected a host of abbreviations and acronyms are prevalent throughout the document, as well as technical terminology rather specific to MRA. These are well covered by the list of abbreviations and the glossary. It is advisable that the list of abbreviations be moved forward to follow the preface. Early familiarity with the abbreviations will assist in the readability and interpretability of the document given their superabundance in early chapters of the MRA Guidelines.

Both Appendix A and B are appropriate and have utility and should be retained. If Chapter 3 were to be divided into two chapters, the material questions presented in appendix B could be reformatted for an independent chapter on hazard identification.

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

It was suggested in the Introduction that the presentation of the guidelines could be extended to other scenarios such as risk assessment for bioagents, genetically engineered organisms, products of cells, etc. This is a valuable suggestion and based on the material provided would be a natural extension of the MRA guidelines.

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

A more discrete introduction to dose response characterization to include comparatives issues in evaluating J or U shaped response curves (hormesis) could be considered. Discussion of the applications and implications of cost-benefit, risk-benefit, and risk-risk analyses would be appropriate for extending the pathogen MRA to other scenarios.

2. Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

The introduction reads as though it is communicating to multiple audiences beyond the immediate needs of the Agencies' risk assessors, agents and professional (preface paragraph 1) to include a broad range of stakeholders, policy makers and the public. A restatement of the specific audience of the "Guideline" is merited for the start of the introduction. One would expect that risk assessors would be familiar with the rationale for risk assessment (RA) and would not need generalized background. However, if the document is also communicating to others in the policy, academic and informed stakeholder/public arena it should be stated so, rather than offering a rather bland statement to the effect that "the document is offered to provide information that may be useful for microbial risk assessors" (page 1, lines 19 & 20)

What really is meant by "risk analysis" as described on page 2? Is it really Risk Characterization? Figure 1.1 is rather a poor representation of risk analysis, as it would appear that risk analysis should result from the unique intersection the three elements of risk assessment, management and communication described by the figure? The broad representation of risk analysis as an encompassing circle appears arbitrary, as does the general description of risk analysis (page 2, lines 8 & 9) making it questionable whether risk analysis even needs to be a terminology meriting discussion; since it does not appear fully developed elsewhere in the Guideline?

The section dealing with question 1.4, "When can I apply this MRA guideline?' appears fragmented. It recovers ground (page 5 lines 1-7) covered in the preface and also introduces terminology such as "submicrobial" (line 6) of weak scientific lineage or mixed descriptors such as sensitive (line10) vs. susceptibility (line12) with what I believe have common meaning. I would also argue that fish have "life stages" (e.g., larval) but that humans don't (line 6) and that this is better described as "age class". This same section then reintroduces the intent for the guideline (page 5, lines 18-38) containing material

central to the organization of the Guideline (elements from lines 21-31) and this material should be moved forward in the chapter.

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

1.5 A discussion of the differences of Microorganisms and Chemicals (pages 5-8) relative to RA is relevant. However, could this material be summarized relative to hazard characterization and/or dose response relationship with the residual material moving to an appendix?

Figure 1.2 (page 9) appears to have very low information content and could be eliminated as well as references to it elsewhere in the document.

Material from Sections 1.1 lines 25-40, section 1.3, section 1.9 and 1.10 share significant redundancy and unclear target audience. Can this material be consolidated for a general background appendix?

3. Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

This chapter appears rather comprehensive in laying out the rationale, needs and approaches for planning and scoping activities.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

Stakeholder involvement and needs appear well accommodated.

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

Section 2.5.3 could well be moved to an appendix as it does not appear to directly speak to the Food and Waterborne Pathogen MRA issue at hand.

Section 2.6 appears rather central to Scoping and should be moved forward in the chapter.

Section 2.6.2 appears to somewhat of a distraction and is brought forward as an additional concept with limited underpinning. Can this be eliminated without detriment to the document? (yes)

Section 2.6.6 page 35, lines 18-29 appears to be a policy statement rather than guideline for scoping and should be moved to a sidebar, footnote or appendix.

4. Chapter 3 – Hazard Identification and Hazard Characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

The rationale for discussing the combined attributes of the pathogen and potential effects is acceptable. However, the chapter should begin with a clearer definition with hazard identification, e.g., occurrence and potential exposure to an etiological agent (organism capable of causing disease) and/or specific adverse effect (illness). Currently page 43 lines 5-8 are ambiguous. How the issues of epidemiology, surveillance, clinical, etc. define the context of the hazard should then be declaratively stated rather than used as adjectives of hazard identification.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

As indicated earlier, the introduction on page 5 lists HI and HC as two distinct elements in the MRA suggesting each with equal weight in the successful RA. The intent of chapter 3 does appears to diminish this weighting, not by intent, but by failure to clearly discriminate the two elements within the chapter and deferring some of the discussion, quantitatively, to dose response assessment. It is recommended that HI and HC be clearly described independently within the chapter, in defined subsections, and then collectively evaluated a points of intersection. This should be accomplishable if HC is confined to the description "HC focuses on a particular microorganism(s) and potential or known mechanisms of host pathogen interaction, virulence and pathogenicity" (page 43, lines 8 & 9). One such "mechanism" appears wrongly described on page 47 line 42 which should read "such mechanisms can result **from** [rather than in] the horizontal transfer of genes ….."

5. Chapter 4 – Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

In general, the Chapter is well developed and information rich providing a fairly comprehensive treatment of dose response assessment and theoretical framework for modeling. There may be some excess with description of modeling and uncertainty analysis requiring some special expertise to clearly interpret the alternatives provided. The chapter makes a number of good points including the difficulties in equating dose with infection and illness and requirements for monitoring (fecal shedding or serum antibody levels) along with manifestation of clinical symptom. Page 69, lines 14-17 also points to the utility of epidemiological source data and advantages over clinical feeding trials in providing inclusive source data on sensitive populations. While this is a retrospective analysis it can be used to back calculate dose and also provide important insight into host population with realistic phonetic and genetic diversity.

In discussion of dose response modeling, the emphasis is almost exclusively non-threshold modeling approaches from a conceptual framework. Given the somewhat recent re-emergence of hormesis in toxicological modeling (E. Calabrese, 2005. Environ. Pollut. 138:378), it seems appropriate that mention of this topic be made and why it remains untenable in MRA. As human microbiome studies continue to advance, evidence may one day be forthcoming the thresholds and perhaps even beneficial low dose exposure do exist.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

Other than above, nothing else comes to mind.

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

Nothing identified.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

The text of Chapter 4 provides a limited conceptual narrative on these issues and, similar to model description (pages 76-79), reasonable statistical or applied mathematical skill to fully comprehend their implications. Graphical data visualization, plotting different model response curves with and without variability and uncertainty estimates may make the comprehension easier.

6. Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

This is a well thought out chapter and appears quite complete. Section 5.1.12 (page 96) seems to lack and equation to support the parameters mentioned in text paragraph 2. Then on page 97 Eq.5.1 is called out with no mention in text. Presumably the missing equation? The purpose of risk assessment (Section 5.2.1) seems to emerge from nowhere and would be better identified as prospective and retrospective exposure assessment. Section 5.2.5 benefits from the number of illustrations use in describing Scenario Analysis. Section 5.2.6 (page 114, line 40) describes the Center of Excellence in Microbiological Modeling and appears to be out of place and more of an advertisement when examining the URL.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

No comment.

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

This material in many ways is redundant with Chapter 4. It appears that these two topics could be combined for the two chapters. The description itself is good but as suggested in 5D above graphical descriptions make the implications clearer.

7. Chapter 6 – Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

No additional comment needed. Clear and appropriate.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

None to offer.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

Generally well connected; to the point that pages 139-144 seem somewhat redundant.

8. Chapter 7 – Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Clear and well described. No additions needed.

9. Chapter 8 – Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Yes, no additions identified

10. Overarching Issues

10A. Overall utility of the Guideline

Very good, 8 on a scale of 10. Clarity in modeling and uncertainty analysis could be improved

10B. The flow and continuity of the document

7 on a scale of 10. Basic organization framework very good. Chapters 1-5 could be improved too many points of view.

10C. The consistency of the document, both in language and level of detail, across the chapters

Good, 6 on a scale of 10. Chapters 1-5 could be improved to many points of view, uncertain audience, and redundancies and excess information.

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors)

Excellent, 9 on a 10 scale.

COMMENTS SUBMITTED BY

Donald W. Schaffner, Ph.D.

Peer Review Meeting of EPA's Draft Microbial Risk Assessment Guideline:
Pathogenic Microorganisms with Focus on Food and Water

Comments submitted by Dr. Donald W. Schaffner

1. Overall Format

1A. Please review and comment on the usefulness of this format and ease of use.

I found chapter 2 to be useful. Chapter 3 contains some statements that I do not agree with regarding Hazard Characterization (HC). I've always view HC as another name for Dose-Response (DR) modeling, and this is supported in at least some of the literature. This document asserts that HC is different from DR, but is unconvincing. Chapter 3 should be re-written to focus on Hazard Identification (HI). Chapters 4 and 5 are fine, but far too long, and essentially duplicate what can also be found in the literature. Chapter 6 also duplicates what can be found in the literature. Chapter 7 is interesting and potentially useful, but should focus more on tips for risk assessors interacting with risk managers. Chapter 8 seems to imply the risk assessor will be talking with stakeholders or the general public. Chapter 8 should instead provide tips on communicating about risk with risk managers.

1B. Please review and comment on other sections: chapter 1, glossary, abbreviations, references, and appendices. Is their format and inclusion appropriate and useful? (For example, the appendices are a collection of assumptions and questions that may be useful for an assessor to consider – should they be retained in the guideline and/or reformatted in some way?)

Chapter 1 is a somewhat useful introduction, but in the end includes too much unnecessary detail, and fails to make a convincing case for why this document needed to be written and why it needed to be so long. A shorter document that focused on practical tips for those doing microbial risk assessment within a US Federal agency would have been much more useful that a longer document that tried (and failed) to be the definitive reference on MRA.

The glossary, abbreviations, references, and appendices are all quite useful and/or interesting. I wish there had been more of this type of information and less re-hashing of stuff that can be found in other references.

1C. Please review and comment on the suitability of this approach to the overall format presented in the draft guideline.

As noted above, I would have like to have seen more tips on how to do QMRA in a US federal regulatory context, and less re-hashing of what one could easily find in other published documents from Codex, FAO/WHO, etc.

It's not clear what is meant by "application to other scenarios, circumstances and regulatory context" Does this mean bioterrorism? Animal disease modeling? These and other microbial risk related topics are also covered by the peer reviewed literature, expert reports and federal documents.

1D. Please identify and provide the rationale for any suggestions, if any, to make this approach better.

Detailed comments can be found in the page by page summary at the end of this review.

2. Chapter 1 – Introduction

2A. Please review and comment on the ability of this chapter to provide the proper introduction to MRA and to emphasize the benefits for users to apply the Guideline to their risk assessments.

I would question the need for any more than a very short introduction to MRA, and pointers to key references and reports. Detailed comments can be found in the page by page summary at the end of this review.

2B. Please review and identify the presence of superfluous information in the chapter, if any (i.e., could it be shortened? If so, please provide the rationale for any suggestions).

Figure 1.1 can be deleted, some would question its validity (see alternative representations containing "a sea of risk communication). The sections on: What are Some Fundamental Differences between Microbes and Chemicals; What is the Relationship of Infectious Disease to Human Health as Applied in a MRA; What are the Benefits of Iterative MRA could all be deleted.

3. Chapter 2 – Planning and Scoping

3A. Please comment on whether this chapter captures the essential components and level of detailed instructions necessary for planning and scoping, including problem formulation.

This is a very useful chapter, and an essential part of what this document contributes to advancing the field. The CARVER+Shock section is less useful and could shortened or just mentioned by reference.

3B. Please comment on whether this chapter addresses the needs of the stakeholders involved (e.g., risk assessor, risk manager/decision-maker, interested parties).

The document does appear to address the needs of all those listed.

3C. Please identify and provide the rationale for any suggestions, if any, to enhance the utility of this chapter.

Delete the CARVER+Shock section to simply the mention of a reference.

4. Chapter 3 – Hazard Identification and Hazard Characterization

4A. Please review and comment on the appropriateness of addressing both of these elements. Please identify and provide the rationale for any suggestions to clarify this hazard identification even further, if needed.

This chapter should focus only on HI. As noted elsewhere in my comments, I believe HC is essentially DR modeling. I don't agree with much of what is said in this chapter regarding HC. I also disagree with redefining hazards to mean things other than microbial agents. People have a difficult enough time with knowing what constitutes a microbial hazard to re-define it to be other things (like the days spent in a hospital) doesn't help. While the days spent in a hospital might be a key variable in the risk assessment, the hazard is still the microbial agent that one might contact while in a hospital.

Some of what is included in this chapter (e.g., What are the Mechanisms that May Lead to the Development of New Pathogens or Pathogens with New Traits; What Methodological Approaches can be Used to Identify and Quantify Microorganisms; does not appear to be relevant to HI in the context of MRA.

4B. Please review and comment on whether this approach of combining hazard identification and characterization is useful and logical. Please identify and provide the rationale for any suggestions to enhance the utility of this approach, if needed.

Clearly I disagree. I don't find it useful and I don't think it is logical. Much of what the report calls HC could simply be defined as being part of HI. I would be happy to see the term HC go away from dis-use and see it replaced with DR modeling. Redefining HC to make it part of HI prolongs its disappearance.

5. Chapter 4 – Dose-Response Assessment

5A. Please review and comment on whether the discussion for microbial dose-response assessment is appropriate, useful, and understandable.

The material is generally appropriate, useful, and understandable, although I would question the level of detail provided. As noted elsewhere in my comments, this report should provide pointers to the literature, and not attempt to be the definitive reference. The section on "How Can I Model the Spread of Disease in the Population?" appears to be out of scope.

5B. Please identify and provide the rationale for any additional scientifically accepted dose-response models that could be included.

Key omissions from Table 4.1 would be *E. coli* O157:H7 models by Cassin et al, and Powell et al., as well and the FAO/WHO *Salmonella* DR model. Why are no *Listeria monocytogenes* DR models included?

5C. Please comment on whether any specific scientifically accepted animal or in vitro dose-response protocols, models, and methods could be included as tools. If identified, please provide the rationale for their applications and limitations in helping establish human dose-response curves.

Given the impossibility of studying the effect of *L. monocytogenes* on human fetuses, some of Mary Alice Smith's work on *L. monocytogenes* on monkeys could be cited, see Infection and Immunity, February 2008, p. 726-731, Vol. 76, No. 2, Dose-Response Model for Listeria monocytogenes-Induced Stillbirths in Nonhuman Primates, for example.

5D. Please comment on whether the uncertainty and variability in dose-response findings are clearly described in the document. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

Clear enough. Again, trying to be the definitive reference should not be the goal, but rather cite the key references, and references that will be key in years to come and leave it at that.

6. Chapter 5 – Exposure Assessment

6A. Please review and comment on whether the discussion for microbial exposure assessment is appropriate, useful, and understandable.

As with other comments, this section is far too long and tried to be the definitive reference. The government risk assessor would be better served by a shorter chapter that outlines key principles, common problems or pitfalls, ad cites some definitive references. The entire discussion around "source" and "source evaluation" reads like it was written by a water person and poorly shoehorned into a discussion relevant to food. Food MRAs focus strongly on prevalence, which I find oddly missing from this chapter.

6B. Please identify additional scientifically accepted exposure tools, methods, or approaches that could be included to ensure a robust approach to adequately determine the microbial occurrence and human exposure factors relevant to health risks of pathogens in food and water.

I think the chapter has a fairly comprehensive list already. I have suggested some references in detailed comments below.

6C. Please comment on how well uncertainty and variability in exposure assessment are addressed. Please identify and provide the rationale for any suggestions to improve the discussion of these issues, if needed.

Coverage is sufficient.

7. Chapter 6 – Risk Characterization

7A. Please review and comment on whether the detail presented in this chapter is enough to capture the essential information/data in order to conduct a risk characterization. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

Detail is sufficient. As with my comments on other chapters, this chapter could also be shortened, buy it's less excessive that chapters 4 and 5 which need more shortening. The section on model validation is important and useful. I especially like the inclusion of examples. The use of examples is tool which could be emulated in other chapters.

7B. Please identify additional risk characterization guidance available that can/should be referenced.

See detailed comments for suggestions on other references to include.

7C. Please review and comment on whether the chapter provides adequate details on how to apply the findings from Chapters 3 - 5 to complete an appropriate risk characterization as well as address the questions posed during planning and scoping.

Detail is generally sufficient.

8. Chapter 7 – Risk Management

8A. Please review and comment on whether this chapter provides enough information to the risk assessor about how an assessor works with risk managers. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

This was one of the more useful chapters in the report. There are lots and lots of papers and reports that explain DR modeling or Exposure Assessment. There are far fewer reports that help microbial risk assessors communicate with microbial risk managers. This is one area where this report can be a useful addition to published documents on this topic.

9. Chapter 8 – Risk Communication

9A. Please review and comment on whether this chapter provides enough information to the risk assessor about what an assessor should be aware of regarding the communication needs of the risk assessment. Please identify and provide the rationale for any suggestions to enhance the utility of this chapter, if needed.

This is an odd chapter, as it seems to be a general primer on risk communication. There are plenty of examples of other such primers, so the authors should not try to re-invent the wheel here. What would be a useful focus would be to discuss important communication issues around risk that are faced by federal risk assessors. I imagine that most of these relate to communication with risk managers, as well as

communication with stakeholder (at least to the extent that federal risk assessors are allowed to do this). All the text devoted to "informing the public" does not appear to be relevant.

10. Overarching Issues

10A. Overall utility of the Guideline,

10B. The flow and continuity of the document,

10C. The consistency of the document, both in language and level of detail, across the chapters,

10D. Its applicability to stakeholders as well as risk assessors (but keeping in mind, this is written primarily for risk assessors).

There are parts that are useful (most of Chapters 1, 2, parts of Chapters 3-6, most of Chapters 7-11 and the appendices). A significant amount of Chapters 3-6 could be cut and/or rewritten. The document is excessively long. The consistency of the document could be improved, as there is some duplication and repetition. Some sections have excessive detail, while other sections could use more.

I don't see the document as being terribly useful for stakeholders. It's far too long and far too difficult to find what might potentially be useful. I'm not sure it's really going to be all that useful government risk assessors. It's utility for this audience could be improved by cutting away details that can be found elsewhere (and citing that information), as well as by providing tips and suggestions unique to government risk assessment that don't exist elsewhere, or that are hard to find. The tables and other sections that summarize the existing literature and published reports are useful and should be retained.

Detailed, page by page comments follow below. Please note that the page number refers to the physical page number within the document not the numbered page number in the upper right hand corner. For example, the page numbered "Page 1" is actually the 9th physical page in the document. To convert from the physical page number indicated below to the numbered page, subtract 8. Note that "Content" refers to text in the document and "Comment" is my comment on that context. A marked up PDF of the report including all these comments is available on request.

Page 7:

Content: "INTERAGENCY WORKGROUP MEMBERS"

Comment: Why no FDA involvement? CVM and CFSAN have both done microbial risk assessments.

Page 10:

Content: "Figure 1.1 is a representation of how these terms are related."

Comment: Figure 1.1 is one possible representation. There are others.

Page 11:

Content: "This Guideline also is considerably longer and more detailed than the MRA frameworks that precede it (Codex, 1999; ILSI, 2000; Codex, 2007a, 2007b)."

Comment: There are also guidance documents produced by FAO/WHO that should be considered.

http://www.fao.org/docrep/010/a0251e/a0251e00.htm

http://www.fao.org/docrep/006/y4666e/y4666e00.htm

ftp://ftp.fao.org/ag/agn/jemra/MRA17_05.10.09_f.pdf

Page 12:

Content: "Guideline is the result of the collaborations of microbial risk assessors from a number of Federal Agencies"

Comment: Why is FDA missing from this list?

Page 17:

Content: "Often, the lack of data, new data or interpretations, or uncertainty or variability in information will require you to revisit the original charge or premise for conducting a risk assessment."

Comment: Will require _one_ and not _you_? I find the repeated use of “you” in the document to be jarring. I understand this was an editorial decision, but it still seems odd.

Page 17:

Content: "How Does This Guideline Fit in with My Agency’s Current MRA"

Comment: Same comment “With _an_agencies...” would sound better than “With _my_ agencies…”

Page 24:

Content: "See Section 2.3 for an overview of how CFSAN does planning and scoping for major risk assessments."

Comment: And yet CFSAN wasn't involved in writing this document. This continues to puzzle me.

Page 51:

Content: "The HC focuses on a particular microorganism(s) and potential or known mechanisms of host-pathogen interaction, virulence, and pathogenicity."

Comment: Hazard characterization is often synonymous with dose response assessment. That does not appear to be the case for this report.

Page 52:

Content: "For example, the number of days spent in a hospital may be a hazard that correlates with risk of nosocomial infection."

Comment: I disagree. The number of days is not a hazard. The organism causing the infection is the hazard.

Page 52:

Content: "What are Hazard Identification and Hazard Characterization?"

Comment: It seems like this section should come first in the chapter.

Page 55:

Content: "What are the Mechanisms that May Lead to the Development of New Pathogens or Pathogens with New Traits?"

Comment: It's not clear what this has to do with risk assessment.

Page 57:

Content: "Batz et al. (2004) constructed a comprehensive list of pathogens for the Foodborne Illness Risk Ranking Model (FIRRM) analytical software tool using data generated by various federal agencies. This includes estimates of the incidence of foodborne illness by CDC as reported by Mead et al. (1999)"

Comment: Both the Batz reference and the Mead paper have been updated. See comments elsewhere in this review.

Page 60:

Content: "You should be familiar with laboratory approaches for identifying and quantifying the microorganism(s) of concern."

Comment: Why?

Page 69:

Content: "Qualitative evaluation (hazard characterization) of a pathogen is also included in the conclusions drawn with regard to potential health impacts, particularly if data for a quantitative MRA are not available."

Comment: Hazard characterization and dose-response assessment are often used interchangeably. This should be noted here.

Page 71:

Content: "due to the potential for pathogen growth in some foods prior to consumption,"

Comment: This phrase belongs at the end of the sentence.

Page 76:

Content: "Clearly document what sources of data were considered, utilized, and omitted, and provide justification for those decisions."

Comment: This is an absolutely essential piece of advice, and it would also bear repeating in the exposure assessment section of the document.

Page 77:

Content: "Epidemiological information also can be used to calibrate dose-response curves derived from animal data with respect to the relevant human response range; this was done in the FDA/USDA/CDC Listeria monocytogenes risk assessment by shifting the mouse mortality dose-response curve based on human mortality rates attributed to L. monocytogenes (FDA/USDA/CDC, 2003)."

Comment: I believe this was also done in the FDA vibrio risk assessment.

Page 78:

Content: "How Can I Model the Spread of Disease in the Population?"

Comment: This needs to be integrated and harmonized with the similar section in the next chapter. It's really part of exposure, not dose response.

Page 80:

Content: "3) Discuss limitations of models"

Comment: Give examples of limitation to be helpful.

Page 80:

Content: "4) Articulate strengths/weaknesses and advantages/disadvantages of the models"

Comment: How is this different than limitations?

Page 82:

Content: "E. coli O157:H7"

Comment: Cassin et al. too

Page 83:

Content: "Salmonella"

Comment: FAO/WHO too?

Page 84:

Content: "4.2.1) as the most relevant for microbial dose-response assessment."

Comment: Why most relevant? Beta Poisson is often used.

Page 86:

Content: "One-stage or hierarchical models can be fit to the data using methods that include Markov Chain Monte Carlo Simulation (MCMC)"

Comment: This needs integration with the MCMC discussion in the next chapter.

Page 94:

Content: "Other resources that provide overviews of exposure assessment are those by the"

Comment: See also The Modular Process Risk Model (MPRM): a Structured Approach to Food Chain Exposure Assessment, by Maarten J. Nauta in the ASM book edited by Schaffner.

Page 94:

Content: "WHO/FAO (2008),"

Comment: Cite correctly, FAO first.

Page 96:

Content: "a) How many viable pathogens (or indicators) are present at the source (e.g., infected chicken, contaminated carcass) at time zero?"

Comment: Odd phrasing that I would never use for food. Sounds like we are talking about water.

Page 96:

Content: "d) At what rate are they released? 1) Counts/unit time (e.g., cfu, pfu, genomes per minutes, seconds, hours, days)"

Comment: Food people would be concerned with prevalence too.

Page 97:

Content: "a) water activity, b) pH, c) carbon source, d) electron acceptor, e) sunlight intensity, f) temperature,"

Comment: Why list these in this manner? Why not in a sentence?

Page 103:

Content: "If dependent variables are mistakenly assumed to be independent in a Monte Carlo analysis, the likelihood of common occurrences in the real world may not be correctly estimated via simulation."

Comment: Can you give an example of mistakenly assumed independence?

Page 106:

Content: "a) What are the substantial scenarios?"

Comment: What does substantial mean in this context?

Page 106:

Content: "Are you really this certain about all of this?"

Comment: Are you really certain this is a good sentence?

Page 109:

Content: "(simple as possible, but not simpler)."

Comment: Cite Einstein.

Page 113:

Content: "a) Young children (up to 10 different age groups (EPA, 2005) b) The elderly c) Persons with compromised immune systems d) Pregnant women e) Chronic smokers f) Military personnel (deployed and non-deployed) g) Occupationally exposed individuals"

Comment: Why a list, why not a sentence?

Page 114:

Content: "Attribution Modeling"

Comment: This section contains no references. I suggest citing work by the Danes (i.e., Tina Hald) and/or CDC (Painter et al.).

Assessing the Differences in Public Health Impact of Salmonella Subtypes Using a Bayesian Microbial Subtyping Approach for Source Attribution, Sara M. Pires and Tine Hald and. Foodborne Pathogens and Disease. February 2010, 7(2): 143-151. doi:10.1089/fpd.2009.0369.

Recipes for Foodborne Outbreaks: A Scheme for Categorizing and Grouping Implicated Foods, John A. Painter, Tracy Ayers, Rachel Woodruff, Elizabeth Blanton, Nytzia Perez, Robert M. Hoekstra, Patricia M. Griffin, and Christopher Braden. Foodborne Pathogens and Disease. December 2009, 6(10): 1259-1264. doi:10.1089/fpd.2009.0350.

Page 124:

Content: "You can apply more complex growth and attenuation models in exposure modeling. For example, the Gompertz equation – or modifications thereof – includes specific parameters for lag time and asymptotic maximum density (Haas et al., 1999)."

Comment: Many predictive microbiologists are using the Baranyi model these days.

International Journal of Food Microbiology, Volume 23, Issues 3-4, November 1994, Pages 277-294. A dynamic approach to predicting bacterial growth in food. József Baranyi , Terry A. Roberts.

Page 125:

Content: "To more completely assess all possible exposures, it may be necessary to consider possible secondary transmissions that result from a primary infection. Such an approach commonly requires consideration of a disease transmission model."

Comment: How would a risk assessor determine if a secondary transmission model was needed?

Page 126:

Content: "(WHO/FAO, 2008)."

Comment: Citation is FAO/WHO, 2008

Page 138:

Content: "For further detail and discussion on risk characterization, good references are the NRC reports (NRC, 1983, 1994, 1996, 2009), EPA's Risk Characterization Handbook (EPA, 2000a), and An Examination of EPA Risk Assessment Principles and Practices (EPA, 2004b)."

Comment: See also FAO/WHO document.

Page 140:

Content: "Risk characterization consists of two principal steps—risk estimation and risk description."

Comment: Reference needed. I've never heard of this as a formal division.

Page 142:

Content: "Consider 1) that in the light of uncertainty and default choices, your agency may proceed in the direction of more public health protection compared to less protection."

Comment: Which would be a risk management decision.

Page 154:

Content: "WHO/FAO 2008"

Comment: Cited as FAO/WHO by convention.

Page 154:

Content: "Researchers gathering data for the USDA use the more formal rigorous definitions of verification and validation as follows (Oscar, 2005):"

Comment: I'm not sure that a single research citation by a USDA ARS researcher should be used to speak for all USDA, as this sentence would imply.

Page 156:

Content: "The NRC ―Red Book initially defined risk management in very broad terms as ―the process of evaluating alternative regulatory options and selecting among them."

Comment: Broad yet quite government centric. Corporations have risk managers too, and they don't evaluate regulatory options.

Page 158:

Content: "When and How Can Risk Managers be Involved in Risk Assessments?"

Comment: I would also recommend the excellent chapter Using Risk Analysis for Microbial Food Safety Regulatory Decision-Making, by Sherri B. Dennis, Janell Kause, Mary Losikoff, Daniel L. Engeljohn, and Robert L. Buchanan from Schaffner 2008.

Page 162:

Content: "For chemical risk assessment usually the risk level is stated quantitatively. For microbial risk level, regulators very often refer to quantified risk reduction, without actually stating the level of risk associated with the risk reductions or commenting on the acceptability of the level of risk."

Comment: Why is this?

Page 163:

Content: "(e.g., low- acid canning regulations)"

Comment: Give citation?

Page 165:

Content: "(Sellnow, 2008; Morgan, 2002; Lundgren and McMakin, 1998)."

Comment: See also Hallman's chapter in the ASM book edited by Schaffner that appears in the bibliography of this report. Hallman's discussion of the topic is fairly unique, as he specifically discusses risk communication on microbial risks. His chapter is entitled “Communication about Microbial Risks in Foods”

Page 165:

Content: "Inform the public about risk"

Comment: Really there are many publics: the general public and many different stakeholders.

Page 165:

Content: "and the public."

Comment: Again, many publics...

Page 166:

Content: "all persons who produce and consume"

Comment: It would also include people that handle ground beef (e.g., restaurants, supermarkets)

Page 169:

Content: "—Salmonella."

Comment: Italics

Page 170:

Content: "How In-Depth Can I Communicate?"

Comment: Awkward phrasing

Page 175:

Content: "See OMB (2003) for full descriptions of cost-benefit analysis and CEA."

Comment: Surely a short definition could also be supplied here?

Page 176:

Content: "hazard identification"

Comment: Why is hazard characterization missing from the list?

Page 177:

Content: "infectious dose"

Comment: This definition should mention median infectious dose or ID50.

Page 182:

Content: "Variability is usually not reducible by further measurement of study, but it can be better characterized."

Comment: In contrast uncertainty CAN be reduced by further study. Should this be added to definition on uncertainty above?

Page 182:

Content: "measurement of study,"

Comment: _or_

Page 186:

Content: "Batz. (2004) Identifying the most significant microbiological foodborne hazards to public health: a new risk-ranking model. Food Safety Research Consortium, Discussion Paper Series, Number 1, September 2004. http://www.rff.org/RFF/Documents/FRSC-DP-01.pdf"

Comment: A more current citation would be: http://www.rwjf.org/files/research/72267report.pdf

Page 198:

Content: "Mead, P.S.., Slutsker, L., Dietz, V., McCaig, L.F., Bresee, J.S., Shapiro, C., Griffin, P.M., and R.V. Tauxe. (1999) Food-related illness and death in the United States. Emerging Infectious Diseases 5(5):607-625. http://www.cdc.gov/ncidod/EID/vol5no5/pdf/mead.pdf"

Comment: The Scallan 2011 papers from CDC are more current references on this topic than Mead et al.

Papers are entitled:

Foodborne illness acquired in the United States—major pathogens

Foodborne illness acquired in the United States—unspecified agents.

Both published in Emerg Infect Dis. 2011

Page 204:

Content: "World Health Organization/Food and Agriculture Organization (WHO/FAO). (2008) Microbiological Risk Assessment Series 7 - Exposure Assessment of Microbiological Hazards in Food – Guidelines. http://www.fao.org/docrep/010/a0251e/a0251e00.htm"

Comment: Recommended citation format for joint FAO/WHO Documents is to cite FAO first. See recommended format text after clicking the link.

Appendix E: Observers

Peer Review Meeting for EPA's Draft Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water

L'Enfant Plaza Hotel
Washington, DC
November 7, 2011

Observers

Nicholas Ashbolt
Senior Research Microbiologist
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Scott Biernat
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Association of Metropolitan Water Agencies (AMWA)
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Thomas Carpenter
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Kerry Dearfield
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U.S. Environmental Protection Agency
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Appendix F: Meeting Agenda

United States
Environmental Protection Agency
Office of the Science Advisor, Risk Assessment Forum

Peer Review Meeting for EPA's Draft Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water

L'Enfant Plaza Hotel
Washington, DC
November 7, 2011

Agenda

8:00 AM	Registration/Check in
8:30 AM	**Welcome, Introductions, Meeting Purpose & Agenda** ..... *John WIlhelmi, ERG (Contractor)*
8:45 AM	**Public Comment** ..... *John Wilhelmi*
9:00 AM	**PEER REVIEWER DISCUSSIONS (Charge questions 1, 2, and 3)** ..... *Darrell Donahue (Chair) & Reviewers*
	Introductory Remarks (1) Overall Format (2) Chapter 1 – Introduction (3) Chapter 2 – Planning and Scoping
10:30 AM	**BREAK**
10:45 AM	**PEER REVIEWER DISCUSSIONS (Charge question 4 and 5)** ..... *Darrell Donahue* (*Chair) & Reviewers*
	(4) Chapter 3 – Hazard Identification and Hazard Characterization (5) Chapter 4 – Dose-Response Assessment
12:15 PM	**LUNCH**
1:15 PM	**PEER REVIEWER DISCUSSIONS (Charge questions 6, 7, and 8)** ..... *Darrell Donahue (Chair) & Reviewers*
	(6) Chapter 5 – Exposure Assessment (7) Chapter 6 – Risk Characterization (8) Chapter 7 – Risk Management
3:00 PM	BREAK

Agenda (cont.)

3:15 PM	**PEER REVIEWER DISCUSSIONS (Charge questions 9 and 10)**	*Darrell Donahue (Chair) & Reviewers*
	(9) Chapter 8 – Risk Communication (10) Overarching Issues	
4:00 PM	**Development of Conclusions and Recommendations**	*Darrell Donahue (Chair) & Reviewers*
4:50 PM	**Closing Remarks**	*John Wilhelmi*
5:00 PM	ADJOURN	